MAKING SENSE *

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THE meaning of words has a profound effect on the progress of medicine; for words, though they provide a vehicle by which thought can travel, seldom allow it to arrive intact at its destination.

Facts and Words

It is pleasant to believe that the facts of clinical medicine exist quite independently of the names we bestow upon them; but this is not so. In clinical medicine it is not only a matter of finding words to fit the facts, but often of finding facts to fit the words. When christening a baby we wait for the child to be born and then find a name for it. When christening a disease we wait for the name to be born and then we try to find a disease for it. With children we announce their names in the Births columns of the lay Press and with diseases we announce their names in original articles of the medical journals. The only difference is that children's names have to be registered. There is no Medical Registrar-General of Terminological Births and Deaths—only medical dictionaries and the *International List* of classified diseases. Those who compile these publications collect medical terms but do not supervise their creation. They include many terms that ought to be painlessly put away.

There is something about a name, particularly an eponymous term, which brings into being things which never seemed to be there before.

"In the beginning was the word."

Take, for example, Pel-Ebstein fever. Every student knows that cases of Hodgkin's disease may show a fever that is high for one week, low for the next week, and so on. Does this phenomenon really exist at all? I think it very unlikely indeed. Yet if one case of Hodgkin's chanced to run such a temperature, the news would soon travel round:

"There's a good case of Hodgkin's disease in Galen Ward. You ought to have a look. It shows the typical Pel-Ebstein fever."

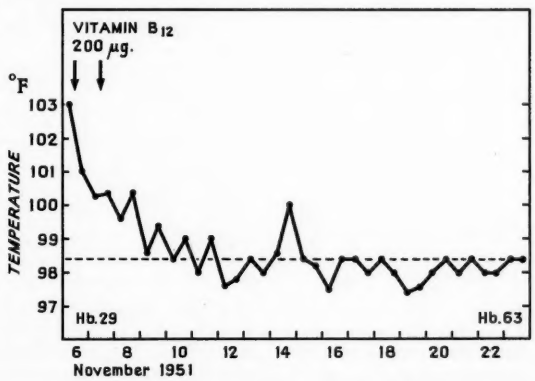
The chart might be copied for teaching purposes, or even put in a book. The naming of a mythical fever leads inevitably to its occurrence in textbooks. One popular textbook for nurses depicts particularly classical temperature charts, attributed to various fevers. I asked the author how many hospital notes she had searched before she found such beautiful examples. "Oh, there was no trouble about that," she replied; "I made them up out of my head." I wonder whether other fevers in textbooks have similar origins.

It does not matter whether or not Pel-Ebstein fever exists, my contention remains the same: the bestowal of a name upon a concept, whether real or imaginary, brings it into clinical existence.

I looked up both Pel's [1] and Ebstein's [2] original papers. They described chronic relapsing fever probably due to brucellosis; there was nothing to suggest Hodgkin's disease in their cases, nor did they mention it.

A good example of creation beginning with the word is gallstone colic. There is no such thing.[3] Colic is a pain continuously waxing and waning, like the colonic cramps of food-poisoning. Gallstone pain steadily climbs to an agonising peak without any fluctuation and then passes off. But so firmly has the label colic been stuck on to this pain that the pain is expected to be colic, assumed to be colic, believed to be colic and finally bullied into being colic, and a patient with gallstone pain will be described as having colicky pain however steady it may be.

Contrariwise, a condition without a descriptive term has far less chance of clinical recognition. A rose without a name may smell as sweet, but it has far less chance of being smelt. Supposing we take an unnamed fever and an unnamed pain to contrast with the examples I have given. In untreated pernicious anæmia there is often quite a high fever. 60% of my cases with red-cell counts below $1^1/_2$ million per c.mm. show a fever over 101°F. This usually settles to normal levels within two or three days after an adequate dose of vitamin B_{12} (see figure). I



make no claim that this fever is of great importance, but I do assert that had it been called the Addison-Castle fever or hypocyanocobalaminic fever every medical student in the land would have heard of it, many doctors would be afraid to diagnose pernicious anæmia without its presence, and the proportion of patients with this fever would rise sharply once the name got into nurses' textbooks (because if they did not show the fever they would have their thermometers put back in their mouths until they did).

Now for a pain without a name. Have any of you ever had a very brief, sharp, needle-like pain, near the apex of the heart; acutely localised to one point seemingly inside the chest wall, but feeling as if something was adherent to it? Breathing sharpens it, so there is often a disinclination to take a deep breath while it lasts. It comes out of the blue, it passes off in a few minutes, and although acute it is not at all distressing.

* From the second Lettsomian lecture for 1959, delivered before the Medical Society of London on Feb. 9. An abbreviated version of the first Lettsomian lecture is to appear in the *British Medical Journal*, and the three lectures will later be published together in the *Transactions* of the society.

1. Pel, P. K. *Berl. klin. Wschr.* Jan. 5, 1885, p. 3.
2. Ebstein, W. *ibid.* Aug. 1, 1887, p. 565.
3. French, E. B. Unpublished paper read to the Association of Physicians, Edinburgh, 1957.

If you have encountered anything closely resembling this, will you please hold up your hands? [Over a third of the audience held up their hands.]

As you see, this condition seems to exist; yet, because it has no name, it has no clinical existence, so we cannot discuss it. Whether it should be named I am unable to say. The naming of diseases ought not to be undertaken lightly. A fertile medical author can easily beget a large clinical progeny; but some of his youngsters may turn out to be illegitimate, and with others there may be doubt about their paternity.

A special kind of disease-naming is done by those branches of industry whose sales depend largely on the planned creation of non-existent diseases, such as night starvation, hidden hunger, and tired blood. In this highly creative and imaginative work the importance of a good name cannot be exaggerated. One weekly paper ran a competition for an advertisement introducing a new disease with a patent medicine to cure it. Here are a few extracts from one of the winning entries:

> "Have you shoddy juvicles? Do you moil at night and wake prinkling, with a throbble? You are almost certainly suffering from GLOIDS. Waste no time. Write immediately in strict confidence for our free booklet prepared by a well-known Harley Street doctor. Mark envelope Dr. X. GLOIDS. Dept. KZ. All enquiries treated with strictest confidence."

Although this may treat patent-medicine disease as a joke, it is a serious matter. We do not know how many bowel neuroses are initiated by relentlessly persuading the public into vain strivings after inner cleanliness.

I have only once named a disease and that was Munchausen's syndrome. I discovered nothing about it; I only described something that most doctors knew already and gave it a name. Yet the effect of christening it astounded me: case-reports, articles, and correspondence on the subject have continued ever since, both here and abroad; new names are added to make it more confusing, and new explanations offered for its occurrence (in America the allegation has been made that it is only caused by the National Health Service). Finally, a psychiatrist and a psychologist have been making a special study of it for over four years; they have a flying squad standing by for twenty-four hours a day ready to collect cases from anywhere in the country. They keep them in for months (to the great benefit of the community) and they ask them what different-shaped ink splodges remind them of (with less definite benefit to the community).

There are many syndromes that have no name. For instance, there is no name for an unexplained bout of fever and malaise lasting two or three days and commoner in children than in adults. The layman calls this "flu"; but the doctor, who correctly prefers to reserve this term for the pandemic condition caused by an identifiable virus, is powerless when faced with this condition. P.U.O. is properly reserved for more lengthy fevers. In hospital, the consultant occasionally takes refuge by filling in the diagnosis as flu and then putting inverted commas round it to show he is unhappy. In his own home, when one of his family gets it, he is worse off. He mutters vaguely:

> "Take an aspirin or two and it'll clear up in a few days. It's nothing much. Just one of those things."

If this does not satisfy his wife, he may be driven by sheer nomenclatural bankruptcy to call in a colleague to show his wife that another doctor cannot do any better.

Thus words perpetuate illnesses, syndromes and signs whose existence is doubtful, deny recognition to others whose existence is beyond question and distort textbook descriptions to conform to the chosen word. It is worth pursuing the subject a little further.

Power of Words

An ancient and important property of names is that they give to those who know them a feeling of power over what is named. However uninformative the name of his illness may be a patient feels his foe is partially vanquished once he knows its name. We all know the conversation:

> "I seem to have an inflamed tongue, doctor. Will you have a look at it?"
>
> "Ah, yes. You've got glossitis."
>
> "Thank you, doctor. It's all right now I know what it is."

Ogden and Richards [4] point out that every country has its story of a name that has to be discovered before an evil can be dispelled or a foe vanquished. Probably the best known of these is the story of a dwarf called Rumpelstiltskin who was able to claim a queen's first-born child unless she could find his name. With such an unusual name, he was understandably (but mistakenly) confident of success. It is not a name a nicely brought-up girl would be likely to know, for it means "crinkly foreskin".

Similar stories abound in international folklore depending on the idea, that knowing the name of a thing gives power to him who knows it.

> "What is this strange skin condition with red rings which expand from the centre in widening circles?"
>
> "That", says the dermatologist, "is erythema annulare centrifugum."

He has spoken the words of power, and the dignity of the profession has been upheld.

Other words appear to hold power against the patient. If you tell a woman she has rheumatism, she asks, fearfully and tentatively:

> "But is it arthritis, doctor?"

The significance of words to our patients is a subject on which systematic research could gainfully be pursued. Arthritis appears to portend a protracted and crippling disease which will leave a man deformed and helpless, whereas rheumatism betokens a few aspirins, a bottle of liniment, and back to work next week. But names give comfort as often as despair, providing an illusion of clarity where there was mystery and giving a tangibility to illness which makes it more likely to be overcome. This applies both to patients and to doctors. The penetrating mind of Matthew Arnold saw through the emptiness of a name and in his poem *A Wish* he wrote:—

> Nor bring to watch me cease to live
> Some Doctor, full of phrase and fame
> To shake his sapient head and give
> The ill he cannot cure—a name.

I may seem to imply that words only provide comforting illusions, or suitably opaque coverings for ignorance. That is not my intention; but I believe it essential to be aware of the defects and limitations of the medical vocabulary before it can be successfully used.

The Meaning

The study of meaning is a subject so surrounded with difficulties and contradictions that few people dare speak about it confidently. The only exception was Humpty Dumpty, whose views were admirably clear and confident:

> "When I use a word", Humpty Dumpty said in a scornful tone, "it means just what I choose it to mean, neither more or less."

4. Ogden, C. K., Richards, I. A. The Meaning of Meaning; p. 26. London, 1923.

"The question is", said Alice, "if you can make a word do that."

"The question is", said Humpty Dumpty, "which is to be master, that's all".

This Humpty Dumptyrian attitude is not enough for medical semantics. When we use a word it has to mean the same to us as it does to the person we are addressing or else our thoughts are not transmitted intact. Consider the meaning of meaning as it applies to some words in the medical vocabulary.

First, there is the *etymological* meaning. For example, take the word "meconium", which means poppy.

Secondly, there is the *implicational* meaning, the notions either true or false upon which the etymological meaning is based. In this case that meconium causes drowsiness as poppy seeds do, and also that the fœtus in utero is kept asleep thereby.

Thirdly, there is the *referential* meaning. In this case, the black stuff in a baby's colon.

I chose this word because there is little doubt about its meaning today. But this is a matter of luck. Had it followed its original derivation it might have come to mean "the opiates present in the fœtal stools". Then the word would have died as soon as there was general agreement that the fœtal stools contain no opiates. Had the word taken another turn it would have meant "that substance which keeps a fœtus asleep in utero"; various theories as to its composition might have arisen and discussions taken place on whether a fœtus sleeps in utero.

Take another word—micturition. Here there are two distinct meanings:

1. The correct meaning according to scholars and the *Oxford Dictionary*. This is: "a morbid frequency of urination".

2. The meaning which is fixed in the minds of ninety-nine medical men out of a hundred: "the act of urination".

Academically there is no doubt about it. Miction is the proper technical word for urination (from the Latin verb *mingo, mingere, mixi, mictum*). Micturio is a different word, bearing the suffix -urio common to desiderative verbs which all belong to the 4th declension and express urgent desire (see *Kennedy's Latin Primer*, para 132); but does that matter much? We all misuse the word, and understand each other perfectly. To say miction would be shorter and neater, and, what is more, would be proper. (To use the Biblical word would be even shorter and even neater, but would be *im*proper.) Once a word has been mishandled consistently, it is useless for scholars to try to preserve its correct meaning. Like a bolt screwed into the wrong socket, it forces a place for itself and at the same time spoils the thread of the seating so that the correct fitting will no longer go in properly.

The importance of keeping words undamaged by handling them carefully and putting them in the right place only is one that needs underlining. But, once misused, they are spoilt for ever. We have said lymph "gland" so long that the word "node" is becoming a pedantic interloper. We use hemiplegia and hemiparesis so carelessly that their nice discrimination between complete paralysis and weakness can no longer be preserved. Again, "aphasia" properly signifies complete loss of word comprehension, in contrast to dysphasia, which signifies only partial loss; but nowadays to read that a patient is aphasic gives you no idea whether his speech defect is gross or mild. The way we use this word is about as foolish as calling all degrees of weakness "complete paralysis".

Which, then, is the true meaning of a word: is it the dictionary definition or the sense in which it is used? There is no answer to this question, because it depends on what you mean by the true meaning of a word. We are now getting into the deep and muddy waters surrounding the meaning of truth and the meaning of meaning, and approaching a realm of metaphysics and semantics in which I feel most uncertain. Yet I ask you to bear with me if I wade about in them a little longer.

Christening by Conjecture

There are far subtler problems of meaning than those arising from mishandled words. Consider the apparently straightforward term "ruptured plantaris syndrome". We all know it means the collection of symptoms caused by rupture of the plantaris muscle. And, what is more, we all know the syndrome. There is sudden pain in the calf—so sudden that the sufferer, if walking in the street, looks round to catch the urchin who threw a stone at him. A few hours later the calf is black and blue, and it remains painfully swollen for weeks. The name seems admirable too, does it not? No obscurity, no difficult words, no doubts.

But you are wrong. There is the most profound obscurity, there is the greatest difficulty, there are the most grievous doubts. An abominable semantic crime has been committed: a single term has been knowingly applied to two completely different things without making the slightest effort to determine whether the one is equal to the other, or even related to the other. A pathological process and a collection of symptoms have been given the same name.

Supposing a man suggested that the terms "tic douloureux" or "trigeminal neuralgia" should be changed to "the hypopineal syndrome" because he was sure that the symptoms were due to hypofunction of the pineal gland. You would say politely:

> "Perhaps we ought to wait a bit. Are you quite sure that hypopinealism is the sole cause of this face pain?"

Even if the man could produce a wealth of evidence to strengthen his contention, a philosophical clinician would say:

> "Well, I suggest you define hypopinealism as the underfunctioning of the pineal gland, whether or not it produces any symptoms, and keep the terms trigeminal neuralgia to describe a particular kind of facial pain, whatever the cause of that pain may be. Then, if you are right, the textbooks can say 'Trigeminal neuralgia is usually caused by hypopinealism', but if you are wrong and hypopinealism is found to cause no illness except hyperemesis gravidarum, our heritage of accepted medical terms remains unscathed.
>
> "But", says our imaginary pinealist, "if that were shown to be so, would you then suggest that the term hyperemesis gravidarum be replaced by the term hypopinealic vomiting?"
>
> "Heaven forbid!" replies the clinical philosopher. "We are rarely perfectly certain of the cause of anything; so if we name things according to their supposed causes, whether they be conjectural or indubitable, so shall we have to change the name of the thing if it turn out to be not so caused. And, moreover, we should have to change the name of that cause too, because, having been forced into an improper association with a group of symptoms to which it should never have been connected it would have become so corrupted by them that it would be unsuitable to return to its proper place in the medical vocabulary. We do not call sciatica the lumbar-disc syndrome, despite our view on its cause, and that is why the words 'sciatica' and 'lumbar-disc protrusion' are safe from defilement should other

causes for sciatica be found or different effects of lumbar-disc protrusion be discovered. St. Paul said to the Thessalonians (and it applies to pinealists too): ' Prove all things; hold fast to that which is good.' And Socrates said in *Cratylus:* ' He who first gave names and gave them according to his conception of the things which they signified; if his conception was erroneous, shall we not be deceived by him ?'[5]"

Thus ends the indignant peroration of our imaginary clinical philosopher, as he finally disposes of the foolish pinealist.

I return to the ruptured plantaris syndrome, from which this argument developed. It illustrates a fault in nomenclature which causes more trouble than any other of the semantic abuses which are committed by medical men. Because the name of a pathological process (rupture of the plantaris) has been placed upon a syndrome (sudden unexplained pain and bruising), we are in an impossible position. We do not know to which it applies —the pathology or the symptoms—and so we are convinced, unthinkingly and uncritically, without a shred of evidence, that the one causes the other. It is immaterial to my argument whether or not rupture of the plantaris muscle does really cause these symptoms; yet all the same you may be interested to learn that it almost certainly does not. I have searched the literature and found one genuine case of ruptured plantaris muscle[6] (N.B.—I mean muscle, not syndrome):

A young soldier complained of a painless lump in his calf which he noticed five months after being kicked on the calf muscle. A sarcoma of the calf was suspected, the calf was explored, and a ruptured plantaris muscle was found, curled up into a ball accounting for the lump. It was removed and the man had no more trouble.

I also found innumerable cases of the ruptured plantaris syndrome, but in none of them was there any evidence that the plantaris muscle had ruptured. I was interested to learn, as I followed my researches into the literature of the 1880s, that W. G. Grace suffered from this condition; but in those days it had other names like tennis leg and ruptured gastroenemius.

If I labour the point I apologise, but I am convinced it is of great importance. To name a thing by its supposed cause, whether or not that cause is the right one, is a very serious mistake. To label by conjecture, instead of by observed facts is neither necessary or profitable. I am quite happy with the word myxœdema (which means " a jelly-like swelling ") and do not wish to call it hypothyroidism even though I believe that hypothyroidism is almost certainly its cause.

The ramifications of causal names are unending. As the *Book of Job* has it:

" Who is this that darkeneth counsel by words without knowledge ?"

When I was a student, blood beneath the dura mater was not called subdural hæmatoma but pachymeningitis interna hæmorrhagica. This convinced everyone that it was caused by inflammation and held up the discovery that head injuries caused subdural bleeding which can be surgically treated. Take another example. We all see middle-aged women with restless, painful, arms, worse at night and worse after doing the washing. It is a common condition and nobody really knows what causes it. Yet according to the wide varieties of cause which are suspected —so is it given as many names. Brachial neuritis, the costoclavicular syndrome, the scalenus-anticus syndrome, cervical rib, the carpal-tunnel syndrome. This is impossibly silly. If this condition had some reasonable name like " nocturnal brachialgia " then we could profitably discuss whether it was caused by a neuritis or by costoclavicular compression or by compression of the median nerve in the carpal tunnel. But to name it the costoclavicular syndrome and then to discuss whether the costoclavicular syndrome is caused by carpal-tunnel compression makes no sense, anatomically or physically. However sure of a cause clinicians may be, a diagnostic label must be descriptive and not causal.

Targets, Navels, Mexican Hats, and Bowls

Other types of conjectural naming are equally troublesome.

In hæmatology cells are often named by what is guessed about them instead of what they look like. (I apologise for the words " what they look like." No proper pathologist ever reports what anything looks like—he only reports what it " is morphologically indistinguishable from.") Though we know a lot of what red cells do, we still call them red cells—an admirable term. Other cells are less fortunate, for instance those red cells which may be found in obstructive jaundice, sickle-celled anæmia, and other conditions. Instead of a pale centre these have deeply stained centres and thus show alternate dark and light concentric zones. About 1936, A. M. Barrett, who was a fellow student with me, became interested in them. He sensibly called them " target cells [7]" which describes them well, and involves no conjecture about why they look like this or what properties they have. Someone else thought they looked like navels and called the abnormality " umbonation " which, though more fanciful, is at least not conjectural. But soon afterwards two Americans[8] noticed these cells and likened them to Mexican hats: not from their appearance in stained films, but from their ideas of what they would look like if they could be seen alive. " They do not look like Mexican hats ", they implied, " but we are sure they would, if we could see them as they really are."

The modern view is that these cells are abnormally thin and bowl-shaped; hence their ability to hold more fluid without bursting than any other red cells can do. So today, when a hæmatologist sees a cell which looks like a target he calls it a thin cell—i.e., leptocyte—though he cannot perceive that it is thin. Barrett sensibly named them by their appearance, even though he thought they were thin. The modern hæmatologist, instead of describing in English what he can see, prefers to describe in Greek what he can't. This is confusing because the appearance of target cells is observed but their thinness and shape is estimated. Appearances do not change as much as estimations. The Mexican-hat merchants estimated that the target cells were of normal thickness, but unduly fragile to weak saline, which is the opposite of the modern view. Had they named target cells by these estimated properties we should be in a worse muddle. In naming anything, some unchangeable attribute of that thing should be chosen to name it by.

The other day I saw a report mentioning leptocytes, which was just going to a general practitioner. I tried to imagine how the perfect practitioner was expected to reason:

" Ah yes, ' leptocytosis '—thin-cells. He guesses they were thin, because he believes they would hold a lot of water —because he thinks they would be shaped like bowls (or

5. Jowett's translation.
6. Croce, E. J., Carpenter, G. K. *J. Bone Jt Surg.* 1944, **26**, 818.
7. Barrett, A. M. *J. Path. Bact.* 1938, **46**, 603.
8. Haden, R. L., Evans, F. D. *Arch. intern. Med.* 1957, **60**, 133.

Mexican hats)—if he was only able to see what their shape was (which he can't). In other words he saw a red dot in the centre of some of the cells. Yes, that's all perfectly clear."

Hæmatologists cannot be prevented from thinking, but they could separate their observations from their conjectures. They could report " target cells present ", and then go on to say what the significance of this might be. The role of a pathologist is not to be a seer. His role is to peer. Gazing into a microscope is different from gazing into a crystal. Yet hæmatological prophesy is rampant, particularly in obscure leukæmias. Controversy on whether cells are myeloblasts, lymphoblasts, or monoblasts is unavoidable, because instead of naming them by their appearance the hæmatologist inspects the artificially dyed, corpses of grossly abnormal, newborn recently deceased white cells, smeared on a piece of glass, and then prophesies what they might become if they were to grow up (which they can't). No wonder then that when some unidentified blood-cell is found wandering at large, unable to produce positive evidence of its identity, the naming of it provides a good deal of dispute and controversy among hæmatologists. In the first article I ever wrote, some fifteen years ago, I said:

" Let us imagine a child found wandering in the street is adopted by three priests who each christen him separately by the names of Tom, Dick and Harry. One day they meet another three priests who have behaved in a similar fashion with another child whom they have christened Harry, Dick and Tom. Now if those six priests try and have a discussion on the qualities of the two children—whether, for instance, Tom is cleverer than Harry—they are likely to become angry and to settle nothing; and they will probably go home and introduce new words such as protomocyte, pseudodickoblast and megaharryophil." [9]

I do not wish to be carried away from the main course of my argument by floating too far down the blood-stream, so may I remind you that we are considering the meaning of meaning and that hæmatological words provide food for thought on the variety of meanings—etymological, descriptive, and conjectural—which may be attached to them. To appreciate it properly the meaning of the word " leptocyte " requires a considerable knowledge of Greek, toxophilism, omphalology, hydrostatics, and hat design.

The *name* of this cell is target cell, the name is *called* leptocyte. The cell *is* a bowl-shaped cell. Does that remind you of something you read many years ago?

White Knight: Let me sing you a song to comfort you. . . The name of the song is called ' Haddocks Eyes '.

Alice: Oh, that's the name of the song, is it?

White Knight: No, you don't understand. That's what the name is *called*. The name really *is* ' The Aged Aged Man '.

Alice: Then I ought to have said ' That's what the *song* is called '?

White Knight: No, you oughtn't: that's quite another thing! The *song* is called ' Ways and Means '; but that's only what it's *called* you know.

Alice: Well, what *is* the song then?

White Knight: I was coming to that. The song really *is* ' A-sitting on a Gate ': and the tune's my own invention.

Similarly, we could say: " The *name* of this disease is Graves' disease; the name is sometimes *called* exophthalmic goitre; the *disease* is called hyperthyroidism; and the disease *is* thyrotoxicosis. Four names for the same condition. This is difficult for students and spoils words we need for another purpose. We need the term exophthalmic goitre to describe the not uncommon association of staring eyes, with goitre but without any thyrotoxicity. (By the way, notice I said " staring "—a very useful word which covers the lid-retraction, the exophthalmos, and the increased glitter from the moist eyeball, which together comprise staring. Most of you probably write exophthalmos when you mean staring. The idea that a long word is more accurate seems to be inborn. For example I am sure you rarely use that accurate and short word " stroke ". No, you write down cerebral thrombosis, cerebral hæmorrhage, or cerebral embolus, according to your fancy, though you have little idea how to tell one from the other; even at postmortem pathologists may be uncertain. Though there is this short word which covers all three, you choose a long word which describes a guess. It is odd. I suppose it is the dislike of sharing words with the laity.)

9. *Lancet*, 1943, i, 213.

Some Foibles of Physicians

As a physician, I have been trying to direct your scrutiny to some of the motes that lie in our brother hæmatologists' eyes, but I must not deflect your attention from the beams that lie in the physicians' own eyes.

Physicians, too, indulge in conjectural names which cause a great deal of confusion. When a physician writes " diminished air entry at the right base " he does not believe that any less air is entering the right base; he only means that the breath sounds are fainter there. Yet when a physician feels sure the lung is solid and that no air is entering it he never uses the words " diminished air entry ". He may describe bronchial breathing or ægophony, but he would never consider writing diminished air entry.

This is not an idle statement. I circularised a number of my physician friends as well as fifty recently elected fellows of the College of Physicians living in England. Of the 37 doctors who said they used the expression " diminished air entry ", 23 admitted that they never meant what they said, and 25 also revealed that when they really believed less air was entering the lung they would not dream of saying " diminished air entry." Even when we say left ventricular failure, how sure are we that the left ventricle is failing? We use the word to describe a collection of symptoms with no certainty that failure of the left ventricle causes them.

If a room goes dark, we may rightly guess it means a power-station failure, but it would be rather stupid always to call darkness " power station failure ". It is wiser to say what we know. In this case we could have a word implying " acute dyspnœa and frothy pink sputum "—rather than calling it left ventricular failure.

Other Bad Words

What other troubles arise from words? Consider that deceptive, but convenient noun—the word " mind ". Because it has been christened with a substantive it is easy to think of it as possessing substantival size or shape or substance, whereas it is really a convenient term used to embrace thinking, believing, remembering, fearing, loving, behaving. and all the hundred and one processes which compose it. The mind has no more existence than the sight, the hearing, or the digestion; it is much more a process than a thing. But being named like a thing it is wrongly treated like a thing. Attempts are made to partition it as if it were as solid as a boarding-house, and psychiatric architects erect jerry-built cubicles within it, into which they invite as lodgers those shady Middle European refugees—the Ego, the Super Ego, and the Id.

Similar structural alterations are eagerly erected by the laity, who regard the subconscious mind as a separate, but somewhat improper, establishment contained within their mental maisonette, but only approachable by the back stairs through a locked door to which only hypnotists and psychoanalysts possess a key.

These troubles might never have arisen if this deceptively concrete word had not been allocated to the tissue of enigmatic obstructions we call the mind; but it is too late now to dismantle the rickety mansions erected on this pseudo-concrete base.

Widely collective abstract words are dangerous. Sir John Wolfenden, addressing the English Society recently, remarked how often we hypostasise and attach a word to some vague notion and then suppose the thing exists. He gave as an example the expression "juvenile delinquency", which embraces every kind of antisocial behaviour from stealing a few apples from an orchard to bludgeoning an old lady to death, and mooted whether all juvenile delinquents really have much in common between them. It is so easy to bequeath an all-embracing word upon a wide variety of things and thus convince oneself that they all resemble each other closely. Are we not guilty of much the same thing if we use the word "stress" to embrace all the thousand natural shocks the flesh is heir to? The same word stress is applied to the deliberate crushing or burning of a limb in experimental work on anæsthetised animals but is also used to cover the strain felt by a financier making money on the Stock Exchange. It seems likely that the reaction of most of us to having our legs crushed would be very different from our reaction to making money on the Stock Exchange. Not only has the word "stress" been allowed to run wild, but its headstrong offspring, the adaptation syndrome, has been given equal freedom to roam anywhere and lay claim to any unexplained illness that comes its way.

Many words in the medical vocabulary are unnecessarily confusing. A technical term should clarify and not conceal meaning. Jaundice transmitted by serum is never likely to be confused with that caused by giving serum from a different animal; the name "homologous serum jaundice" is ridiculous, and in the questionnaire to which I referred earlier 20 out of 29 doctors who use the term admitted they have little idea why they did so. Among ill-chosen words, the dietary unit, the Calorie, is remarkable. Although one thousand times larger than the physicists' calorie (which raises 1 ml. of water 1°C), its name is exactly the same except that it is spelt with a capital C. I know well that at least half of you had no idea this was so because my questionnaire showed 25 out of 48 fellows of the R.C.P. thought that food and physics calories were identical. It is not your fault—it is the fault of the word. Until a few years ago I, too, thought they were the same. Then in a thoughtful moment, drinking a large hot cup of tea, I worked out that it was about 10°C hotter than I was and so if my cup held 100 ml. I was getting 1000 calories per cup. In a flash I saw the reason why fat patients never lost weight on my diets and I planned the cold-food cure for corpulence. To find the answer on p. 1 of a schoolboys' elementary physics book was humiliating.

As we all know, there are two kinds of white cell, the lobed and the unlobed. How happy it would be if we could say so. We manage "lobed" all right, by saying "polymorphonuclear", yet we do not say monomorphonuclear for the unlobed whites; not only do we remove the morph, but having done we do not know whether the term mononuclear includes all the unlobed cells (lymphocytes and monocytes) or whether it is another word for monocyte. My circulated inquiry revealed complete confusion: 24 doctors thought mononuclear cells were monocytes, 22 doctors thought they were unlobed cells (lymphocytes or monocytes), and 4 did not know what to think.

I am sure we are more influenced by the vagaries of our vocabulary than we like to suppose; sometimes unconsciously. You talk about nausea and reeching when taking a history, but you never write it down. Why? Because you don't really know how to spell it! If you put r.e.t.c.h., then you think "I've always called that rĕtch when I read it. The idea that you have a word pronounced rēēch if spoken, and rĕtch if you read it, seems so ridiculous that you put the whole matter out of your mind and avoid using the word in writing but only use it in speech.

One kind of verbal ambiguity is so subtle many people are unaware of its influence. Take the sentence—"he feels cold" which can either mean "I perceive cold when I touch him" or "I believe that he is perceiving cold and is desiring warmth". I do not think I am exaggerating when if I say this ambiguity is responsible for many unnecessary deaths. It is much harder to distinguish different things when they have the same name. Failure to distinguish them is responsible for the use of warmth and the treatment of shock. This practice is foolish, ignorant, and dangerous. It is the result of muddled thinking. "He feels cold" say bystanders, touching the flesh of a shocked man: "Let us heat him as quickly as we can". I now quote from Sir Heneage Ogilvie [10]:

> A certain doctor "calls the use of warmth 'the treatment of symptoms'. I was taught that a symptom is something complained of by the patient. . . . The shocked patient does not complain of cold; he desires it, he knows it helps him, and he spends his dying strength in attempting to throw off the blankets and shock-producing electric cradles heaped upon him by well-meaning but ignorant attendants." Yes, words are more important than you think. Two ambiguous monosyllables—"feel" and "cold"—can murder a multitude.

Style

Lastly, I say something about style. I don't care a fig about schoolroom stuff on the difference between phrases and clauses or the distinction between metaphors, similes, and hyperboles. But I do feel strongly about style. It is only a matter of putting down what you have to say in the neatest and most palatable form. And it cannot be done except by taking a lot of trouble in doing it.

Recently a doctor wrote an article about bedwetting in which he wished to draw a distinction between better-educated people who plan a small but successful family and those with lower standards who raise large mediocre families. This is the way he described them (but I have condensed it a good deal).

> "The mobile families described as showing a loose-knit kinship network and shared conjugal roles accept occupational emancipation and its consequences on interpersonal relationships. They determine the number of their children by a critical assessment of their own emotional, social and economic potential, and they strive to create one or two competitively successful children rather than a gregarious egalitarian sibling group."

Well I ask you? When you take your family on holiday, do you say "I am taking my gregarious egalitarian sibling group with me"?

10. Ogilvie, W. H. *Brit. med. J.* 1954, ii, 358.

Long words and esoteric terms have no place in scientific writings, except when they convey more than their shorter equivalents. If you say: "the capillaries of John's skin are dilated by the exotoxin produced by a hæmolytic streptococcus growing in his pharynx" instead of "John has scarlet fever"; though it is longer and less euphonious it is scientifically reasonable, because it conveys more exact information than the bald announcement of the exanthem—just as $\frac{\delta x}{\delta t} = K\frac{\delta x^2}{\delta y^2}$ means "it oozes" but says it very accurately.[11]

The use of esoteric terms is also justified in concealing something hurtful from a patient as when we talk of neoplasm instead of cancer. The late Mr. Robert Milne used to say, "I think this history should be taken *cum grano salis* because there is a possibility of *pendulum plumbi*." When a doctor wishes to inform another that the patient confronting them is rather dull-witted, a useful if anatomically dubious expression is "This patient shows evidence of considerable cerebral stenosis".

Yet, very often, technical words are used which add very little information, and befog the puzzled minds of those who read them. There is much talk today of the degrading effect of reading comics instead of more serious journals. Here are two descriptions of psychopathic personality—one from a serious medical journal and the other from a particularly low comic—that I borrowed from one of my children.

"In defining the psychological use of the term psychopathic personality I assume a pathophysiology of the brain on a multifactorial basis, genetically predisposed in which contemporary systems are malintegrated the one with the other but whose tie with what happened in infancy is historical rather than causative. This agenesia is homologous in its physiological aspects with normal behaviour."

That one perhaps some of you guessed, is the extract from the serious journal. Now I read you extracts from a journal (which I am afraid you cannot get at the Royal Society of Medicine); but the reference is *Top Spot*, Oct. 25, 1958, p. 1. (All the words are in block letters in circumscribed areas within the illustrations which are lavish and colourful.

"This is the story of Charlie 'Hot Fingers' Hart, who liked his guitar, easy lolly, flash suits and smart dames. Charlie chorded his guitar and sang in his gravel voice; his sulky lips pouted, his eyes lidded and his hips snaked."

I wonder which of those two accounts of a psychopath you prefer? Do you altogether blame me that for the rest of the evening, instead of improving my mind by continuing to read that most respectable medical journal, I sat wrapped in the story of Charlie "Hot Fingers" Hart?

Before I close I warn you of a new kind of jargon, whose cotton-wool coils are being wrapped closer around us every day—the jargon of officialdom and the jargon of committees. In this malignant hypertrophy of language, nobody says anything: they "state", or worse still they "intimate that". They never think: they "are of the opinion that". Nobody finishes anything: it is "duly completed". Nobody is paid: they "receive financial remuneration on a 9½/11ths basis". Nobody looks ahead: they "envisage a long-term policy". This language is a waste of duplicating-paper and a waste of time. Incompetence can hide behind its opacity and activity be smothered by its voluminous folds. I warn you of this deadly and contagious miasma. May I personally intimate to you that after due consideration I am of the opinion that it should be an integral part of your basic policy to take due precautionary measures against this obnoxious prolixity?

Conclusion

If I have done anything to convince you that words can either stifle or stimulate the march of science, by their choice and their use, I am well content. I have read you some very poor stuff in the last part of this talk, to show you the deadliness of bad style: you need something better now. As Stevenson says: "Bright is the ring of words when the right man rings them"; so I read you a few lines of good English to leave you with a pleasant sound in your ears. The right man who is ringing them is William Harvey:

"I tremble lest I have mankind at large for my enemies, so much doth wont and custom become a second nature. Doctrine, once sown, strikes deep its root, and respect for antiquity influences all men. Still, the die is cast, and my trust is in my love of truth, and the candour of cultivated minds."

11. Haldane, J. B. S. Possible Worlds; p. 227. London, 1927.

THE LOCAL COMPLICATIONS OF INTRAVENOUS THERAPY

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THOUGH intravenous therapy is undeniably a great advance, it is not without danger. Most of the complications are trivial and consequently tend to be neglected or set on one side as a necessary disadvantage of a lifesaving method of treatment; but occasional disasters are also seen. They call for a careful assessment of the risks and of the means whereby these may be reduced.

Thrombophlebitis

If an infusion is run into a peripheral vein by way of a needle, metal cannula, or short length of plastic tubing, sooner or later a painful inflammatory condition will develop, spreading proximally from the tip of the needle. The vein progressively thromboses; the infusion slows down and eventually stops, and the vessel is gradually converted into a knotty cord in which pain and tenderness may persist for many months. Some veins probably recanalise within a year or more; but the process reduces the number of those available for infusion during the rest of the illness and may hamper infusions at a later date.

Various factors have been thought important in causing this condition. If the rare case of contaminated infusion fluid (Michaels and Ruebner 1953) is excluded, there is no doubt that the duration of the infusion is the most important factor (Handfield-Jones and Lewis 1952, Medical Research Council 1957). When infusions are limited to twelve hours thrombophlebitis is rare; but the incidence rises steeply after that, rates varying from 40 to 73% being reported (Bolton Carter 1951, Handfield-Jones and Lewis 1952, Page et al. 1952, Jones 1954, Medical Research Council 1957). Four factors determining its onset are the site of infusion, the nature of the infused solution, injury to the wall of the vein by the point of the

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TABLE I—COMPLICATIONS OF INFUSIONS INTO THE LONG SAPHENOUS VEIN OF MORE THAN TWENTY-FOUR HOURS' DURATION

Complication	Number
Phlebitis of any degree	88 (*100%*)
Major phlebitis: more than 6 cm. of vein involved	29 (*33%*)
Severe sepsis requiring incision	1
Septicæmia	1

needle, and the equipment through which the infusion is administered.

Site of Infusion

Most clinical workers now agree that the long saphenous vein and other vessels in the lower limb are ill suited to intravenous therapy (*Lancet* 1955). Table I shows that thrombophlebitis is distressingly common and, because even minor degrees of painful phlebitis in the leg may be incapacitating, we have now abandoned this site for infusion.

Trauma from the Needle

If technique is adequate and immobilisation secure, trauma from the point of the needle can be only a very minor factor. We inserted standard blood-transfusion needles filled with physiological saline solution and with the hub sealed by a short length of latex tubing into the forearm veins of 6 convalescent patients. At the end of seventy-two hours only 2 showed local signs of irritation, and this was very slight.

The Infused Solution

It is a common observation that dextrose in any concentration is more liable to produce thrombophlebitis than most other solutions. This points to some property of dextrose which may be relevant to the causation of thrombophlebitis in general; and it also permits the design of a standard technique for the production of experimental thrombophlebitis in man.

What has been thought to make dextrose particularly irritant are the changes brought about by heat sterilisation

TABLE II—COMPARISON BETWEEN FILTER-STERILISED AND HEAT-STERILISED INFUSION FLUID

No.	Infusion of fluid sterilised by filtration		Infusion of fluid sterilised by heat	
	Duration (hours)	Reaction	Duration (hours)	Reaction
1	17	Severe	24	Mild
2	24	Mild	23	Mild
3	36	Severe	36	Severe
4	10	Mild	28	Severe
5	24	Mild	24	Mild
6	24	Mild	24	Mild

—the decrease in pH to about 3·5–4·0, and the production of small quantities of chemical substances of the furfural group. The influence of these changes can be tested by a comparison of heat-sterilised and cold-sterilised dextrose—an investigation first suggested by Prof. A. W. Wilkinson.

The standard preparation used was an infusion of 6% dextrose at the rate of 125 ml. per hour for twenty to thirty hours into a vein on the dorsum of the forearm through a plastic giving set and a Frankis Evans cannula. The test solution was infused at a similar rate into the opposite arm of the same subject and usually (unless the onset of thrombophlebitis precluded this) for the same length of time. Significant phlebitis was said to exist when redness, swelling, and tenderness extended for more than an inch beyond the tip of the needle or cannula; and the technique could be relied on to produce phlebitis in most subjects if ordinary heat-sterilised dextrose was used. Cold-sterilised isotonic dextrose was prepared by Berkefeld filtration with appropriate precautions. Its pH was between 5 and 6 in every case.

Table II shows that, while formal statistical significance cannot be claimed, cold-sterilised dextrose is, if anything, slightly more prone to produce phlebitis than its heat-sterilised counterpart. We think it unlikely, therefore, that either chemical change in the dextrose or alterations in its pH are important in causing phlebitis. This is in keeping with the finding that buffered solutions do not prevent an inflammatory response (Bolton Carter et al. 1952, P. F. Jones, personal communication).

Equipment

Equipment has already been exhaustively investigated, and it has been clearly shown that some types of rubber tubing contain substances which are irritant (Handfield-Jones and Lewis 1952), and that the incidence of thrombophlebitis can be reduced significantly by the use of latex rubber or more effectively by vinyl plastics (Medical Research Council 1957).

TABLE III—EFFECT OF HEPARIN ON INFUSION PHLEBITIS

Case	Duration of infusion (hours)	Area of thrombophlebitis without heparin	Area of thrombophlebitis with heparin
1	26	5×8 cm.	5× 6 cm.
2	40	5×2 cm.	3×15 cm.
3	43	2×9 cm.	2×10 cm.
4	27	6×9 cm.	2× 8 cm.
5	28	3×8 cm.	4×11 cm.
6	31	2×9 cm.	2×11 cm.

Prophylaxis

Both heparin (LeQuesne 1957) and hydrocortisone (Polak 1956) have been advocated as a means of preventing infusion phlebitis. The thrombophlebitis-producing technique described was used to study the effects of both.

Heparin was administered in the dose recommended—200 units per 100 ml. infused fluid—which is insufficient to produce general heparinisation. The dose of hydrocortisone was chosen arbitrarily at 1 mg. per 100 ml. to avoid risks from systemic effect.

Tables III and IV show the result of six trials of each substance: as before, the other arm of the same patient acted as the control. Heparin is without effect but hydrocortisone definitely reduces the incidence and severity of the condition. The latter drug or one of its analogues (prednisolone is at present being investigated) may thus have a place in the prevention of thrombophlebitis when infusions must be prolonged beyond twenty-four hours. The use of heparin for this purpose should be discontinued: not only is it ineffective but serious accidents have resulted from the erroneous administration of large doses to patients after operation (I. S. R. Sinclair, personal communication).

Caval Catheters

Whenever a needle or other instrument is inserted through the skin, sepsis is a possibility; and it is surprising that infection is not more common. Minor sepsis is often found at the site of a cut-down; but, in our experience, serious effects from it are rare except in the lower-limb veins. Far more serious are the infective hazards of polyethylene cannulæ introduced deep into the vascular

TABLE IV—EFFECT OF HYDROCORTISONE ON INFUSION PHLEBITIS

Case	Duration of infusion (hours)	Area of thrombophlebitis without hydrocortisone	Area of thrombophlebitis with hydrocortisone
1	24	1·75×1·75 cm.	Nil
2	24	1·5 ×0·5 cm.	Nil
3	24	2·5 ×4·5 cm.	2·5×2·5 cm.
4	44	4 ×9·5 cm.	Nil
5	40	4 ×8 cm.	3×8 cm.
6	36	3 ×9 cm.	2×7 cm.

TABLE V—COMPLICATIONS OF CAVAL CATHETERISATION

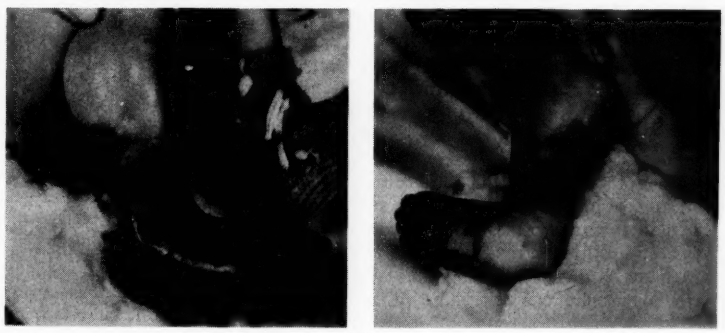
No.	Age (years)	Sex	Primary condition	Site of introduction of catheter	Complication	Outcome	Contribution of catheter to outcome
1	2 mos.	M	Severe gastroenteritis: electrolyte imbalance	R. leg	Staphylococcal septicæmia; septic thrombosis of inferior vena cava	Died	Probable
2	45	F	Crohn's disease: multiple intestinal fistulæ	L. leg	Staphylococcal septicæmia; septic thrombosis of iliac vein	Died	Definite
3	63	M	Carcinoma of stomach: mediastinitis from anastomotic leak	L. arm	Staphylococcal septicæmia; thrombosis of subclavian vein	Died	Probable
4	18	F	Traumatic œsophageal fistula	L. arm	Staphylococcal septicæmia; partial thrombosis of innominate vein	Died	Probable
5	69	M	Perforated duodenal ulcer: peritonitis	L. arm	Staphylococcal septicæmia	Died	Cause of death
6	62	M	Gastrectomy for perforated duodenal ulcer: electrolyte imbalance	R. leg	Staphylococcal septicæmia	Died	Probable
7	58	M	Gastrectomy for perforated duodenal ulcer	L. arm	Staphylococcal septicæmia	Died	Cause of death
8	55	F	Hepatic coma	R. arm	Staphylococcal septicæmia	Recovered	—
9	39	M	Carcinoma of stomach: electrolyte imbalance	R. arm	Thrombosis of axillary vein; pulmonary embolus	Died	Cause of death
10	28	F	Extensive burns	L. leg	Thrombosis of common liliac vein	Died	—
11	51	M	Fistula after gastrectomy	L. arm	Thrombosis of innominate vein	Recovered	—

system. Caval catheterisation is a gratifyingly simple means of administering intravenous fluids for long periods, and in special circumstances such as anuria it may save the patient's life; but it is far from devoid of risk.

Over a period of four years we have carried out approximately 130 caval catheterisations and have also seen the results of many others. Like Artz (1954) and Indar (1959) we have found at necropsy soft clots in the vessels through which the cannulæ had been inserted; but we have regarded them as a terminal phenomenon in the seriously ill patient. Nevertheless, we have encountered both in our own cases and in the practice of others several instances of obstructive thrombophlebitis; and, of even graver import, cases of septic clot formation with septicæmia. These misfortunes are summarised in table v. In our own experience the incidence of serious complications is approximately 4%.

In all patients in whom complications occurred the catheters had been inserted by open operation; but in our personal cases this operation was carried out in the theatre or its annexe with full sterile precautions. We indicate in the table the probable importance which we attach to the caval catheter as a cause of death. In only 1 patient (case 10) could it be entirely absolved from blame. In this respect our experience is similar to that of Moncrief (1958) and of Indar (1959), and 12 examples of septicæmia have been recorded by Hassall and Rountree (1959) after the use of polytheylene tubing for intravenous work.

These major disasters lend emphasis to our earlier statement that caval catheterisation " is a serious undertaking and is quite unsuitable for the occasional operator " (Dudley 1958). It seems unlikely that the use of nylon in place of polyethylene, as suggested by Steele (1959), will greatly alter this conclusion.



Gangrene after infusion into the saphenous vein of an infant (case 3, table VI).

While in some cases sepsis at the site of insertion of the cannula was the obvious cause of the complications, in others the entry wound was clean and dry. In all the cases of septicæmia, however, there was severe uncon-

TABLE VI—VASCULAR COMPLICATIONS OF INTRAVENOUS INFUSIONS INTO LONG SAPHENOUS VEIN

No.	Author	Age	Sex	Primary condition	Fluid infused	Complication	Final outcome
1	Present series	1¾ years	M	Extensive scalds	Plasma	Ischæmia of lower leg and foot	Died
2	Present series	3½ years	F	Multiple injuries	Various, including blood and plasma	Ischæmia of skin of lower leg	Died
3	Present series	3 months	M	Pyelitis	Hartmann's solution	Gangrene of lower leg	Below-knee amputation
4	Dudley (1949)	3 years	F	Extensive scalds	Plasma and saline	Ischæmia of leg and foot	Died
5	Cohen (1948)	Infant	..	Gastroenteritis	Electrolytes	Gangrene of leg	Died
6	Cohen (1948)	Infant		Gastroenteritis	Electrolytes	Gangrene of leg	Died
7	Miller and Sebeck (1955)	15 months	F	Syphilis	Not stated	Gangrene of foot	Died
8	Miller and Sebeck (1955)	6 months	F	Gastroenteritis	Various	Gangrene of leg	Died

trolled sepsis in some other part of the body; and it is tempting to suppose that the septic thrombophlebitis had its origin in a bloodborne infection which took hold on the sterile clot around the catheter, just as it sometimes takes hold on a damaged heart valve. Accordingly, we now limit the use of caval catheterisation to cases free from sepsis, local or distant.

Vascular Lesions

Although the saphenous vein is an undesirable site for intravenous therapy, it may have to be used when one has to establish a route for the rapid administration of fluids to an infant or child. Occasionally this leads to serious vascular complications.

The first definite example was described in 1949 (Dudley 1949), although Cohen (1948) had previously mentioned the condition in another connection. 2 cases have also been recorded by Miller and Sebeck (1955); and we have since encountered 3 more (table VI and figure). In 2 other patients—an adult and a child—we have seen vascular spasm in the limb, with disappearance of pulse and blanching of the skin, spreading from the line of the saphenous vein, during an infusion of blood or of plasma. The skin temperature in the adult fell, with rapid return to normal when the infusion was stopped.

The ætiology of the condition remains obscure; but either spasm in the thick-walled muscular saphenous vein, with spread into the arterial tree (Dudley 1949), or retrograde perfusion of the limb through arteriovenous anastomoses (Cohen 1948) seem the most likely causes. Whatever its cause, the condition can be prevented by avoiding rapid or pressure transfusions into the saphenous vein.

Conclusions

It may seem that by bringing together so many complications we have drawn an unjustifiably gloomy picture of intravenous therapy, or that we have been particularly unfortunate in its use. Nevertheless, it is our impression that the local complications of intravenous therapy are not always recognised and that the experience of others is similar to our own. We have restricted our review to infusion of substances which are commonly administered, omitting the hazards of giving drugs such as noradrenaline.

The prevention of local complications depends not only on careful technique but also on the avoidance of methods which are in themselves dangerous—for example the use of the long saphenous vein. The mitigation of minor complications, such as thrombophlebitis, is largely a matter of limiting the use and duration of intravenous therapy.

All who use parenteral routes should appreciate that they have at their disposal a sharp but two-edged weapon with which as much harm as good can be done.

For permission to study and to report cases we are indebted to Sir James Learmonth, Prof. R. W. B. Ellis, Mr. J. J. Mason Brown, Mr. A. B. Wallace, Prof. John Bruce, and Mr. T. McW. Millar; for access to necropsy material to Dr. N. MacLean; for case details to Dr. J. W. Farquhar; and for the preparation of cold-sterilised dextrose and much other helpful advice to Prof. J. W. McLeod and Dr. I. D. E. Storey.

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ASSESSMENT OF CALCIUM EXCRETION FROM THE URINARY CALCIUM/CREATININE RATIO

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HYPERCALCURIA occurs in a number of clinical disorders, and its presence in any given patient may therefore be of some diagnostic value. When the urine-calcium output is extremely high—500 mg. per 24 hours or more—there is no difficulty in concluding that hypercalcuria is present, but when the excretion is rather less it may be difficult or impossible to decide whether it is abnormal. For this reason many clinicians make use of the technique first suggested by Albright et al. in 1929, and measure the 24-hour urine-calcium after a number of days of low-calcium intake. But this is laborious, it cannot be applied to outpatients with any degree of precision, and the issue may still remain in doubt because there is no agreed figure for the upper limit of the normal range. I have attempted, therefore, to determine whether a low-calcium diet is necessary in assessing urine-calcium, and to test the usefulness of creatinine output as a physiological "constant" against which calcium might be measured.

Method

Subjects Studied

Random samples of urine were obtained from seventeen inpatients convalescing from acute illnesses after 3 days on a low-calcium diet; from twenty-eight similar patients on the ward diet; and from twenty-six "normal" outpatients on their own diet. 24-hour samples of urine were collected from a further fifty convalescent inpatients on the ward diet. Most samples from inpatients were collected between 8 and 10 A.M., and from outpatients at about 3 P.M.

24-hour Samples

2 consecutive 24-hour samples were collected, and the results were expressed as the mean. 4-day collections were made in the metabolic ward, but were never used for creatinine estimation.

Diet

The low-calcium diet contained 100–150 mg. of calcium. The samples were collected after 3 full days on this diet. The ward diet and home diets were unrestricted, but none of the subjects was having calcium supplements or large amounts of milk.

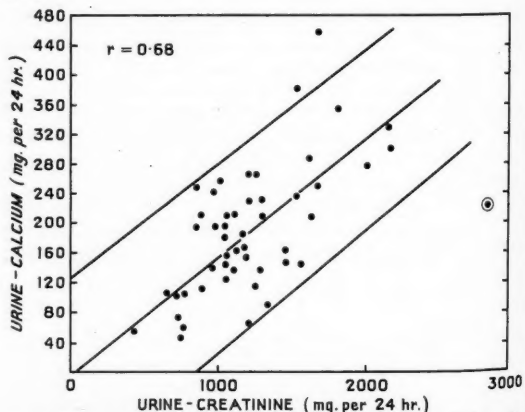

Fig. 1—Mean calcium excretion and mean creatinine excretion in 50 duplicate 24-hour collections on "normal" patients.
(The circled point was not included in the calculation of *r*.)

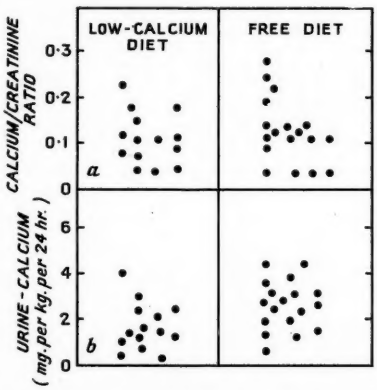

Fig. 2—(*a*) The calcium/creatinine ratio in random urine samples from fourteen normal subjects after 3 full days on a low-calcium diet (left), and in eighteen normal subjects on a ward diet (right); the absolute range is 0·03–0·28. (*b*) The 24-hour calcium excretion and simultaneous calcium/creatinine ratios in the same subjects; the absolute range on the low-calcium diet is 0·5–4·0 mg. per kg. per day, and on the ward diet 0·9–4·5 mg. per kg. per day.

Results

The relation between the mean 24-hour outputs of calcium and creatinine in 50 duplicate collections is shown in fig. 1.

The correlation coefficient is 0·68. The regression of calcium on creatinine and the 95% confidence limits are expressed by the equation $y = 0{\cdot}16x \pm 128$ mg. Because the regression line passes through the origin, it is permissible to express the relation as a calcium/creatinine ratio.

The absolute calcium excretion of the fifty normal subjects shown in fig. 1 ranged from 0·9 to 6·1 mg. per kg. per day. Thus the range of calcium excretion on a weight basis in these fifty subjects was a sevenfold one; the range of the calcium/creatinine ratio (0·05–0·28) was just under sixfold; whereas the absolute range of calcium excretion in this group was 44–455 mg. per 24 hours, which is over tenfold.

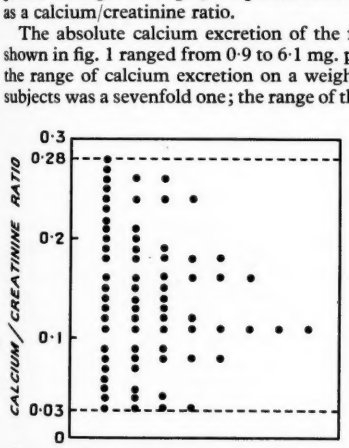

Fig. 3—Calcium/creatinine ratio in 71 random samples from normal subjects.

Fig. 2 shows the ratio of calcium to creatinine (each expressed in mg. per 100 ml.) in the random urine samples from fourteen normal subjects on a low-calcium diet and from eighteen normal subjects on a ward diet.

The range for the low-calcium diet is 0·04–0·23, and for the ward diet 0·03–0·28. The absolute range is very similar in the two groups, but there were slightly more high results in the subjects on a free diet. For purposes of comparison fig. 2 shows also the calcium output in mg. per kg. per 24 hours in the same subjects. The range is again very similar in the two groups, but there are more high figures on the free diet.

In view of the very small difference between the calcium/creatinine ratio on the low-calcium diet and the ward diet, these two sets of results were combined and to them were added a further 39 observations on " normal " inpatients and outpatients, making 71 random urine samples in all as shown in fig. 3. The absolute range of calcium/creatinine is 0·03–0·28.

Table I shows the mean calcium/creatinine ratio, the standard deviation (S.D.), the statistical " normal range " (2 standard deviations either side of the mean), and the absolute range in each of the three groups of random urine samples and in 50 duplicate 24-hour collections. The mean calcium/creatinine ratio and the range on the low-calcium diet are a little lower than on the home and ward diets, but all 121 observations are embraced by the range 0·03–0·28. The 24-hour collections yield very similar results to the random samples.

Diurnal Variations

In five normal subjects, the calcium/creatinine ratio was measured on 4-hour samples of urine throughout the 24 hours. In none of these did the ratio rise above or fall below the range 0·03–0·28 (fig. 4).

Relation to 24-hour Urine-calcium

The calcium/creatinine ratio was measured 84 times in thirty-four patients with miscellaneous disorders on various levels of intake who were in the metabolic unit, and it was compared with the simultaneous 24-hour urine output of calcium, expressed in mg. per kg., calculated from the concurrent 4-day collection of urine (fig. 5). There was good correlation between these two methods of assessing urine calcium ($r = 0{\cdot}75$). It will be noted that most points within the suggested normal calcium/creatinine range (shown by the horizontal lines) also fall within the range of 0·5–6·1 mg. per kg. per 24 hours, which appears from the data in fig. 2 and from the 50 duplicate 24-hour collections to be the corresponding range of absolute urine-calcium output, although fig. 6 is based on a completely different set of data.

TABLE I—DATA FROM RANDOM URINE SAMPLES AND 50 DUPLICATE 24-HOUR COLLECTIONS

Diet	No. of subjects	Sample	Mean calcium/creatinine	S.D.	Statistical normal range	Absolute range
Low-calcium	17	Random	0·123	0·056	0·01–0·23	0·04–0·23
Ward	28	,,	0·132	0·065	0·00–0·25	0·03–0·28
Home	26	,,	0·165	0·070	0·03–0·31	0·05–0·28
Ward	50	24-hour (mean of 2)	0·155	0·055	0·05–0·27	0·05–0·28
All subjects	121		0·147	0·065	0·02–0·28	0·03–0·28

Routine Use of this Method

The calcium/creatinine ratios in eighty-six patients with various metabolic disorders are shown in fig. 6. With the exception of the 2 high values in cases of osteomalacia, all the high and low results were obtained

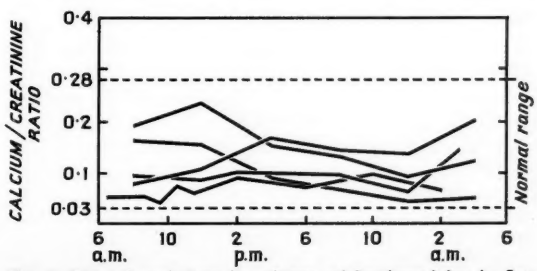

Fig. 4—Diurnal variations in urinary calcium/creatinine in five normal subjects.

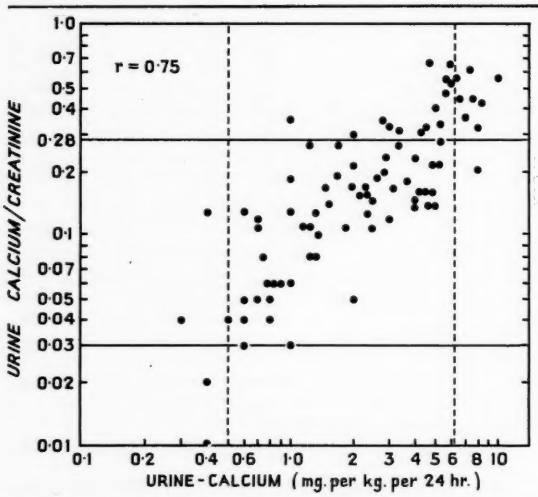

Fig. 5—The relation between urinary calcium/creatinine and concurrent 24-hour urinary calcium output in 84 balance studies on thirty-four patients on various calcium intakes.

(The horizontal lines enclose the suggested normal calcium/creatinine range [0·03–0·28].)

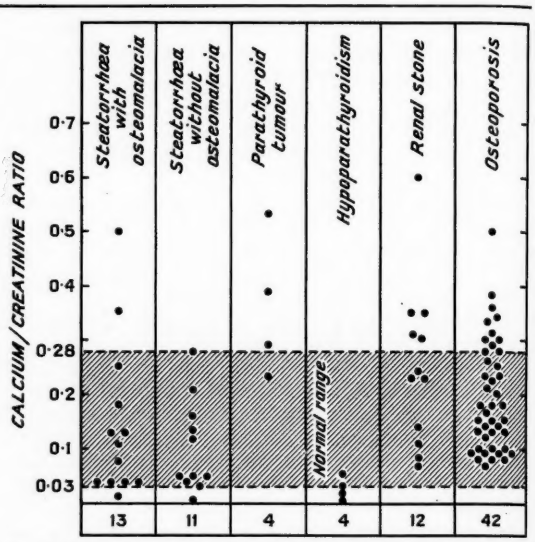

Fig. 6—The calcium/creatinine ratio in random samples of urine from patients with various metabolic disorders which may affect calcium excretion.

in conditions frequently associated with hypercalcuria or hypocalcuria respectively.

500 consecutive observations of calcium/creatinine ratio have been analysed. 325 of these fell within the range 0·03–0·28. 165 observations on forty-eight patients were above this range, and they are summarised in table II. With the exception of one case of biliary cirrhosis, the patients all had conditions or were receiving treatment known to predispose to hypercalcuria. 10 observations on eight patients fell below this range (as shown in table III).

TABLE II—ANALYSIS OF 165 OBSERVATIONS ON FORTY-EIGHT PATIENTS (OUT OF 500 CONSECUTIVE OBSERVATIONS) IN WHICH THE URINARY CALCIUM/CREATININE RATIO WAS HIGHER THAN 0·28

Diagnosis	No. of patients	No. of observations
Osteoporosis	28	46
Biliary cirrhosis	1	28
Hypoparathyroidism (on calciferol)	4	68
Patients on prednisolone	6	10
Primary hyperparathyroidism	1	5
Myeloma	2	2
Renal stone	5	5
Hyperthyroidism	1	1

The diagnosis in every case was one commonly associated with hypocalcuria.

Fig. 7 illustrates the routine use of the calcium/creatinine ratio on a case of hypoparathyroidism seen at frequent intervals over a period of 10 months. The manner in which the calcium/creatinine ratio reflects changes in serum-calcium suggests that this ratio is a valid index of calcium excretion.

Discussion

It has been shown that the ratio of calcium to creatinine in the urine (in mg. per 100 ml.) in a hundred and twenty-one normal subjects on various diets fell within the range 0·03–0·28, the mean being 0·15. The S.D. was 0·065, and the statistical normal range therefore extends from 0·02 to 0·28. I have never encountered a value of 0·02 in a normal subject, however, and I believe that the absolute normal range of 0·03–0·28 is probably more valid.

The measurement of the urinary calcium/creatinine ratio is an empirical procedure. It is not a clearance ratio analogous to the phosphate/creatinine-clearance ratio (Nordin and Fraser 1956). Attempts to consider calcium excretion in clearance terms have not so far proved very successful. In this method, creatinine simply serves as a reference standard by virtue of its relatively constant rate of excretion, but it is a reference standard related to lean body mass (Muldowney et al. 1957) and so perhaps to skeletal mass. The results show that this ratio provides a guide to the subject's rate of calcium excretion. It is more accurate and reliable than the Sulkowitch test (Barney and Sulkowitch 1937), which, though simple to perform, fails to take into account the concentration of the urine sample. This method should therefore be helpful in the diagnostic screening of outpatients, as for example in urological

TABLE III—ANALYSIS OF 10 OBSERVATIONS OUT OF 500 WHICH YIELDED CALCIUM/CREATININE RATIOS BELOW 0·03

Diagnosis	No. of patients	No. of observations
Osteomalacia	3	5
Steatorrhœa	3	3
Uræmia	2	2

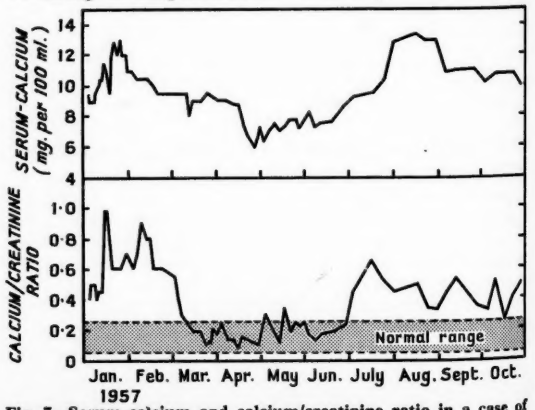

Fig. 7—Serum-calcium and calcium/creatinine ratio in a case of idiopathic hypoparathyroidism seen at frequent intervals as an outpatient over a period of 10 months.

clinics. Its value as an inpatient procedure is more difficult to assess. It is probably no more useful than the measurement of the 24-hour calcium output, if this is expressed in mg. per kg., but it is less dependent upon the accuracy of the collection. But clearly there is great advantage in being able to express calcium excretion in the same way for outpatients and inpatients.

The small difference between the calcium/creatinine ratios in subjects on low-calcium diets and free diets emphasises the relatively small effect of diet upon urinary calcium output, to which attention has already been drawn (Bogdonoff et al. 1953, Nicolaysen et al. 1953, Hodgkinson and Pyrah 1958), but which is not perhaps widely appreciated.

The data of Knapp (1947) show how relatively small changes in dietary calcium affect the mean urinary calcium output in normal subjects; but they also show, as fig. 2 suggests, that in a few normal subjects in any group the urinary calcium output tends to be higher.

The range of 24-hour calcium output in fourteen normal subjects on a 100–150 mg. calcium diet (0·5–4·0 mg. per kg.) corresponds closely to that recorded by Knapp, and the range of 0·9–6·1 mg. per kg. per day in eighteen subjects on a free diet also agrees well with the urine-calcium which she observed in normal subjects on an intake of about 10–20 mg. per kg., which represents the calcium content of an average free diet.

Clearly it is superfluous to institute low-calcium diets for patients whose urine-calcium on a free diet is below 4·0 mg. per kg. per day, since it is already within the normal range for a low-calcium diet, and hypercalcuria cannot therefore be present. Similar reasoning applies to the calcium/creatinine ratio; if below 0·23 on a free diet, it is normal for any diet, and if appreciably above 0·28 on a ward diet it usually remains abnormal on a low-calcium diet (data to be published). On the other hand, no biological standards are absolute, and there will no doubt prove to be patients with ratios around the upper limit of the suggested normal range, in whom a low-calcium diet may be required to establish the presence of hypercalcuria.

Despite this relatively small effect of diet on urinary calcium, very high calcium intakes may raise the calcium/creatinine ratio. Therefore "free" diets must not be taken to include those containing exceptionally large amounts of milk or milk products.

The lower limit of normal urine-calcium output is even harder to define than the upper limit, since normal subjects may have as low an output as is seen in florid cases of osteomalacia. The lower limit of the calcium/creatinine ratio is also less sharply defined than the upper limit, as shown by several cases of steatorrhœa with values within, though usually at the lower end of, the normal range. The occasional case of steatorrhœa with a high calcium/creatinine ratio remains unexplained.

Summary

The mean 24-hour outputs of calcium and creatinine were measured in duplicate on fifty "normal" subjects. The mean ratio of calcium to creatinine (mg. per 100 ml.) was 0·16, and the coefficient of correlation was 0·68.

The calcium/creatinine ratio in random samples of urine in seventy-one normal subjects ranged from 0·03 to 0·28. There was very little difference between the calcium/creatinine range in fifty-four subjects on free diets and in seventeen who had been on a low-calcium diet for 3 full days.

The calcium/creatinine ratio, measured throughout the 24 hours in five normal subjects, did not rise above 0·28 or fall below 0·03.

The coefficient of correlation between the urinary calcium/creatinine ratio and the concurrent 24-hour urinary excretion of calcium in 84 observations on thirty-four subjects on various diets and with various disorders was 0·75.

Measurement of the calcium/creatinine ratio in various clinical conditions revealed a number of values above and below the suggested normal range in those conditions known to predispose to hypercalcuria and hypocalcuria respectively.

I wish to thank Mr. Alex Bell and Mr. Robert Orr for technical assistance.

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THE EFFECT OF TRIIODOTHYRONINE IN NEONATAL HYPERBILIRUBINÆMIA

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AN association between prolonged non-hæmolytic jaundice in the newborn and hypothyroidism has been described (Akerren 1954, Christensen 1956). If the degree of thyroid activity is one of the factors influencing the rate of bile-pigment metabolism, it is possible that infants with neonatal hyperbilirubinæmia, although not hypothyroid, might benefit from the administration of thyroid hormone.

To test this hypothesis we have carried out a controlled trial of the effect of triiodothyronine on the severity and duration of "physiological" jaundice in full-term and premature infants.

The Trial

Two groups of infants were included: 100 infants over $5^1/_2$ lb. birth-weight in whom jaundice appeared during the first 72 hours of life, and 36 premature infants between 2 and 5 lb. birth-weight. Infants of mothers who showed evidence of rhesus immunisation were excluded from the study.

Liothyronine ('Tertroxin') (3 : 5 : 3′-triiodo-L-thyronine sodium) was given to alternate infants. The first 6 full-term babies received 5 μg., and the remaining 44, 10 μg., daily for 5 days after the appearance of jaundice. The prematures were given 5 μg. daily for 5 days from the first day of life. The drug was given by mouth as a single daily dose in a little boiled water or milk.

The first bilirubin determination was performed if possible within 24 hours of birth in the premature infants, and from the onset of clinical jaundice in the mature infants. Levels were estimated daily until the bile-pigment level showed a decline for 2 consecutive days, or a marked fall during one day. Tests were not made on Sundays unless the estimation was clinically desirable.

The specimen for pigment estimation was taken by heelprick. The infant's heel was swabbed with ether, smeared with sterile vaseline, and stabbed with a no. 1 straight suture needle. About

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0·6 ml. blood was milked into a dry heparinised agglutination tube. Total and conjugated bilirubin was estimated on plasma by the method of Lathe and Ruthven (1958). Occasional specimens were stored overnight in the cold before testing.

To guard against possible toxicity, the pulse-rate was observed regularly in the first 10 infants on the drug. Birth-weight and discharge weight were noted in all cases.

ABO and rhesus blood-groups were determined on every mother and infant, and in all instances of ABO incompatibility the maternal serum was examined for the presence of alpha or beta hæmolysins, immune anti-A, or immune anti-B antibodies.

Results

In all, 674 combined determinations for total and conjugated bilirubin were made. The ratio of conjugated to total pigment was similar in treated and control infants. Cases were excluded if the total pigment level failed to rise above 5 mg. per 100 ml., as these were not defined as " hyperbilirubinæmic ".

For infants over $5^1/_2$ lb. birth-weight, the mean peak level of bilirubin in the treated group was 0·8 mg. lower than in the controls (table I), a difference which is not statistically significant. The mean period from birth to peak pigment level was 13·4 hours earlier in the treated babies than in the controls (table I), a difference which is significant ($t=2·3$, $0·01 < P < 0·05$). For premature infants of birth-weight 2–5 lb., the mean peak bilirubin was 2·6 mg. less in the test than in the control group, which is significant ($t=2·07$, $0·01 < P\ 0·05$) (table II). Although the mean period before peak level was 20 hours earlier in the test than in the control group, the result is not statistically significant.

TABLE I—TIME OF OCCURRENCE AND LEVEL OF THE BILIRUBIN PEAK IN INFANTS OVER $5^1/_2$ LB. BIRTH-WEIGHT

Group	No. in group	Mean peak bilirubin level (mg. per 100 ml.)	Mean period from birth to reach peak bilirubin (hr.)
Control . .	50	9·6 ± 0·49	83·7 ± 4·5
Treated . .	50	8·8 ± 0·34	70·3 ± 3·6

TABLE II—TIME OF OCCURRENCE AND LEVEL OF THE BILIRUBIN PEAK IN PREMATURE INFANTS OF 2–5 LB. BIRTH-WEIGHT

Group	No. in group	Mean peak bilirubin level (mg. per 100 ml.)	Mean period from birth to reach peak bilirubin (hr.)
Control . .	18	11·7 ± 0·88	115 ± 9·2
Treated . .	18	9·1 ± 0·89	95 ± 8·8

2 of the control infants and 1 of the treated infants had a positive Coombs test. Mothers of 9 full-term babies in the control series had alpha or beta hæmolysins, including one with immune anti-B. 5 mothers of treated full-term infants had alpha or beta hæmolysins; immune anti-A or anti-B were not detected.

Discussion

For over 40 years evidence has accumulated to suggest that immaturity of the neonatal liver is related to " physiological " jaundice (Driscoll and Hsia 1958).

Billing and Lathe (1956) demonstrated that a major metabolic pathway of bilirubin is that of conjugation with glucuronic acid. Schmidt et al. (1957) have shown that the conjugating enzyme is a glucuronyl transferase present in the liver microsomes.

Vest (1958) found that the excretion of oral acetanilide as *p*-aminophenol glucuronide was greatly reduced in newborn infants, particularly in premature ones. At the same time Lathe and Walker (1958) reported low rates of bile-pigment conjugation in vitro by liver slices from premature babies. Dutton (1959) has found evidence in human fœtal liver, kidney, and placenta of reduced uridine diphosphate glucuronic acid, the precursor of glucuronide synthesis in adult liver (Dutton and Storey 1954, Storey and Dutton 1955), as well as low glucuronyl transferase activity. Brown et al. (1958) have demonstrated a deficiency, in fœtal and newborn guineapig liver, of uridine diphosphate glucose dehydrogenase activity, the enzyme responsible for the formation of uridine diphosphate glucuronic acid.

All these results suggest that a major factor in the production of " physiological " jaundice is functional immaturity of glucuronyl transferase and allied enzyme systems.

A relation between thyroid hormonal activity and the activity of the enzyme responsible for conjugating bilirubin is suggested by the prolonged period of neonatal jaundice in some cretins.

Akerren (1954) cited 10 cases of cretinism associated with jaundice persisting for more than 6 weeks. Jaundice lasting over 2 months occurred in 5 out of 11 cretins in Christensen's series (1956), and in 6 out of 24 cases of cretinism reported by Amlie (1955). Christensen and Akerren do not mention the type of pigment responsible for the jaundice, but the absence of bile in all cases where the urine was examined, and the negative direct van den Bergh reaction, found when the serum of 2 of Akerren's patients was tested, indicate that jaundice in cretins is due to raised levels of unconjugated bilirubin.

Our results suggest that the triiodothyronine may stimulate maturation of the conjugating enzyme, although the actual mechanism of this is obscure. It may be related to an acceleration of oxygen utilisation of the cell, demonstrated " in vitro ", after a 3-day incubation with triiodothyronine, or immediately with the acetic acid analogue, triiodothyroacetic acid (Thibault and Pitt-Rivers 1955). This increased oxygen consumption would in turn promote all the metabolic sequences associated with cellular respiration. Nevertheless a specific action of the drug on the bilirubin-conjugating system cannot be ruled out.

At present exchange transfusion, with its associated dangers, is the only way to prevent kernicterus in the severely jaundiced infant. While rarely necessary in full-term hyperbilirubinæmic infants, a larger proportion of premature babies of this type require transfusion (Crosse et al. 1958). Corner found 25 jaundiced premature infants with kernicterus in a series of 239 consecutive necropsies (Aiden et al. 1950). In none of these 25 cases was there postmortem or serological evidence of hæmolytic disease, sepsis, or biliary obstruction.

Our findings show that, although treatment with triiodothyronine as described will not avoid the necessity for exchange transfusion in most cases it may spare a few marginal cases. Other means of reducing jaundice, such as exposure of the baby to blue fluorescent light (Cremer et al. 1958), have been tried at Queen Charlotte's Hospital. The light treatment was discontinued, however, owing to uncertainty about the toxicity of the products formed from bilirubin by photochemical action (Franklin 1958).

Thus at the moment no alternative to exchange transfusion in severe hyperbilirubinæmia has been found. A solution to this problem must await further work.

Summary

In a trial of L-triiodothyronine by mouth in the treatment of neonatal hyperbilirubinæmia, mean peak bilirubin levels were decreased in both mature and premature treated infants compared with controls, but this difference was statistically significant in the premature group only. The mean period before this peak occurred was also decreased in both treated groups compared with controls, significantly so in the group of mature infants. Infants with rhesus sensitisation were not included in the trial.

Triiodothyronine may act by stimulating the maturation of glucuronyl transferase and other enzyme systems which are responsible for conjugating bilirubin. This may be produced by an acceleration of cellular oxygen utilisation, but a specific action on the conjugating mechanism cannot be excluded.

At the moment, however, there is no alternative to exchange transfusion for the treatment of neonatal hyperbilirubinæmia.

It is a pleasure to express our thanks to Dr. A. W. Franklin, Dr. A. P. Norman, Dr. John Murray, Dr. Merton Sandler, and the research team at Queen Charlotte's Maternity Hospital. We thank also Mr. M. P. Curwen for his advice and help with the statistics. This work was awarded the Board of Governors' research prize for 1958 at Queen Charlotte's Maternity Hospital.

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FIBRINOLYTIC ACTIVITY OF THE BLOOD IN INTERMITTENT CLAUDICATION

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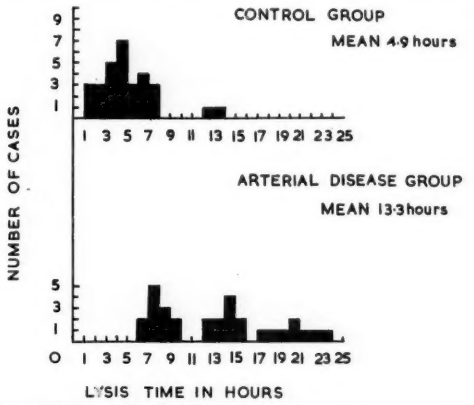
IN atherosclerosis it is important to distinguish between primary change in the arteries and secondary thrombotic occlusion. Patients who have had an occlusion of a major artery are commonly regarded as atherosclerotic, whereas in fact their atherosclerosis may differ little in degree from that found in other people of similar age and sex and living in a similar environment. What distinguishes them are the symptoms caused by intravascular clotting.

The development of these clots depends on many factors. One of these, deficient fibrinolytic activity, has been recognised (Astrup 1956) since Duguid (1949) revived the hypothesis that the intimal deposition of fibrin thrombi may lead to atherosclerosis. Hume (1958) found that in patients who had had a coronary occlusion fibrinolytic activity was depressed for a few days but then returned to normal. Since deficient fibrinolysis has not been previously demonstrated apart from such acute episodes, we compared the blood fibrinolytic activity in patients who had extensive arterial thrombosis with that in subjects without clinical evidence of occlusion. Because patients with intermittent claudication have widespread occlusion of major arteries of the legs (and often develop thrombosis in their cerebral or coronary arteries) they were chosen for study.

AGE-DISTRIBUTION OF PATIENTS AND CONTROLS

Age (years) ..	45–49	50–54	55–59	60–64	65–69	70–74	75–79
Patients with intermittent claudication	2	5	7	7	4	4	1
Controls ..	0	6	6	7	6	4	1



Blood fibrinolytic activity in patients with intermittent claudication and in a control group.

Materials and Methods

Fibrinolytic activity was measured by the method of Fearnley et al. (1957). Whole blood was collected into glass tubes, diluted 1 in 10 with phosphate buffer, and clotted at once by the addition of thrombin at 0°C. The clots were incubated at 37°C, and complete lysis of the clot was the end-point measured. All subjects were fasted for twelve hours before the tests. The blood samples were taken at set times of the day, since there is a diurnal variation in fibrinolytic activity (Fearnley et al. 1957).

30 male patients with intermittent claudication due to atherosclerosis were studied. The diagnosis was supported by femoral arteriography. Patients with diabetes mellitus and essential hypercholesterolæmia, and those who showed clinical evidence of major arterial occlusion within the previous six months, were excluded. The electrocardiograph in some showed ischæmic changes, but none had symptoms or signs of myocardial infarction or cerebral thrombosis. The mean age of this group was 60.

Another 30 men who had no symptoms or signs of peripheral artery disease were studied for comparison: their average age was 61 (table). They were inmates of a home for elderly men and led a largely sedentary life. In this way the difference between the amount of physical exercise taken by the two groups was reduced to a minimum. This was necessary since exercise has been shown to increase fibrinolytic activity (Greig 1956).

Results

The times taken for lysis are shown in the figure. The mean time for the controls was 4·9 hours with a standard deviation of 2·8 hours. The mean lysis-time for the patients with intermittent claudication was 13·3 hours with a standard deviation of 5·3 hours. The scatter was greater in this group, and there was a small overlap into the controls. The difference between the means was highly significant ($P < 0.001$).

Discussion

The exact nature of the fibrinolytic agent as measured by this method is uncertain. Fearnley (1957) believes that it is distinct from plasmin; and, since it is labile in shed blood, he has named it "labile fibrinolytic component". It is partially stabilised by immediate coagulation, and at low temperatures its lability is diminished. Storage tends to reduce its activity, and it displays diurnal variation.

The mean ages of the two groups studied were 60 and 61 years, and it has been shown that in a population selected at random from this age-group advanced atherosclerosis with thrombotic occlusion in the arteries of the legs is very common. This has been demonstrated by

radiological and necropsy studies on subjects who had had no clinical evidence of occlusive arterial disease of the legs (Lindbom 1950, Rodda 1953). Harrison (1953) states that in those who have symptoms the lesions are similar but more severe: in such cases total occlusion of the lower femoral or popliteal arteries by thrombosis is common. The difference between the atherosclerosis of patients with and without clinical occlusive disease of the legs is therefore one of degree and depends on the severity of the thrombosis. Whether the decreased fibrinolytic activity in the diseased group is causally related to their disease requires further study.

Evidence will be presented elsewhere that patients with intermittent claudication have an abnormally high beta/alpha lipoprotein ratio in their plasma (Nestel 1959). The ingestion of fats has been shown to depress fibrinolytic activity in normal people (Greig 1956); and Greig and Runde (1957) have shown that the beta lipoproteins depress fibrinolysis in vitro more completely than the other lipids tested. The decreased fibrinolytic activity found in this study may therefore be one of the consequences of disturbed lipid metabolism which is known to affect blood-clotting in several other ways (Poole 1958).

Summary

The blood fibrinolytic activity was measured in 30 male patients with intermittent claudication and in 30 men of similar age in whom there was no clinical evidence of occlusive arterial disease in the legs. The fibrinolytic activity was depressed in the patients with intermittent claudication.

The possible relation of this finding to the severity and extent of arterial thrombosis and to abnormal lipoprotein patterns is discussed.

I wish to thank Prof. R. R. H. Lovell for his advice and encouragement and Dr. A. J. Barnett for allowing me to see patients under his care.

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IODOPYRINE AS A CAUSE OF GOITRE

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DURING the past five years we have encountered 4 cases in which it seemed likely that a goitre had been caused by taking 'Felsol' powders. These powders, which are quite commonly used by asthmatics (with or without medical advice), are stated by the makers to have the following composition:

Phenazone *B.P.C.*, 0·768 g.
Phenacetin *B.P.*, 0·097 g.
Caffeine *B.P.*, 0·100 g.
Compound of phenazone *B.P.C.*, 0·018 g. and iodine *B.P.*, 0·012 g.
Ext. grindel. liq. *B.P.C. 1949*, 0·003 g.
50% alcohol extract of viscum (10–1) (equivalent to ext. visci *B.P.C. 1923*), 0·002 g.

Evidence will be presented which suggests that iodopyrine (i.e., the compound of phenazone and iodine) was the active goitrogen in the cases we have studied.

Case-reports

Case 1.—A boy was dyspnœic and cyanosed at birth: he had a large goitre. A few days later mother and child were admitted to The Hospital for Sick Children, Great Ormond Street, because it was felt that the infant would require tracheotomy; but his breathing improved spontaneously. At that time the child appeared cretinous. His goitre slowly regressed, but it was still obvious when, at the age of 3 weeks, he was transferred with his mother to University College Hospital. He was bottle-fed but no specific treatment was given. His goitre was no longer palpable by the age of 6 months; and he developed normally up to his present age of 5 years.

Case 2.—The mother of case 1 lived in Durham until the age of 15, and from then on in Sussex. At 13 she developed asthma, which has persisted ever since. At different times she tried various remedies but felsol has suited her best. During the two years preceding the birth of case 1 she took an average of two powders daily.

A normal child was born thirteen years ago.

Her goitre was first noticed ten years before that, but it did not bother her and she never consulted a doctor about it. At the time of her admission to University College Hospital both lobes and the isthmus of her thyroid were easily visible and palpable. The gland felt firm; and, apart from a small nodule, the enlargement was diffuse. Radiography of the neck showed that it dipped into the thoracic inlet. After the investigations which will be described she was given a preparation containing all the constituents of felsol except the iodopyrine. This was somewhat less helpful in controlling her asthma than genuine felsol. During the next year or two she took mainly the felsol without iodopyrine, but resorted to the genuine powders when her asthma became particularly severe. During the past two years her asthma has improved, and she has taken no genuine felsol at all. Her goitre has slowly become smaller, but it is still just palpable.

On admission five years ago she showed no signs of hyperthyroidism; but during the next six months her basal metabolic rate (B.M.R.) rose to +58 (Aub du Bois), she developed tachycardia, she lost 10 lb. weight, and her plasma-cholesterol fell to 134 mg. per 100 ml. She also complained of feeling hot and sweaty, and she was getting palpitations. During the next year this trend was gradually reversed: her B.M.R. and pulse-rate reverted to normal, her weight increased to above its former level, and her plasma-cholesterol rose to 232 mg. per 100 ml. She now appears euthyroid.

It is difficult to explain her transient thyrotoxicosis: possibly it had been kept in check previously by the antithyroid action of iodopyrine.

Case 3.—A woman of 33 was admitted to hospital in March, 1957, with a three-year history of goitre. She had an obvious, firm, diffuse enlargement of both lobes of the thyroid, but no signs of thyrotoxicosis or of myxœdema. She had had asthma for eighteen years and had been taking about three felsol powders daily for 3 years.

After felsol was replaced by a powder containing all its constituents except iodopyrine, she was discharged. Her goitre gradually diminished, and eighteen months later it was no longer visible or palpable.

Case 4.—A woman of 48 was seen in June, 1958. She had had a goitre for fourteen years. In 1949 and 1950 she had been admitted to other hospitals with a view to thyroidectomy, but on both occasions her goitre spontaneously regressed. In 1950 she was started on thyroid extract, gr. 2 daily, because of lassitude and drowsiness; but she showed no objective evidence of hypothyroidism. In 1951 subtotal thyroidectomy was performed and the thyroid extract continued in varying dosage. Between 1951 and 1958 the goitre grew again.

She has suffered from asthma since childhood, and she has taken felsol, up to six powders daily, since the age of 20. In June, 1958, this powder was replaced by one containing all its constituents except iodopyrine. She continued to take thyroid extract, gr. 1 daily. Two months later her gland was no longer visible or palpable. The thyroid extract was then stopped;

TABLE I—UPTAKE OF ^{131}I BY THE THYROID IN CASE 1

Treatment	Percentage of dose in thyroid		
	At 2 hours	At 6 hours	At 24 hours
Nil	5	10	18
Three felsol powders	2	3	4
Three felsol powders without iodopyrine	5	8	14
Three doses of iodopyrine alone	4	6	7

but, though the gland remained small, she felt less well without it. She is now receiving a regular dose of *l*-thyroxine, 0·3 mg. daily.

Investigations with Radioactive Iodine

Case 2 was given a tracer dose of ^{131}I twenty-five days after her last dose of felsol. Three days later she was given three felsol powders and the test was repeated. Five days later she was given three doses of felsol without iodopyrine, and another tracer dose of ^{131}I. Finally, she was given iodopyrine in three doses, equivalent to three felsol powders. The uptake of ^{131}I by the thyroid in these tests is shown in table I: it suggests that felsol inhibits ^{131}I uptake and that iodopyrine is the effective constituent.

In 10 patients with non-toxic goitre not caused by drugs ^{131}I tests were performed, with and without a preliminary oral dose of iodopyrine. In all tests 200 mg. potassium perchlorate was given by mouth an hour after the tracer dose of ^{131}I. This eliminated from the thyroid any ^{131}I that might have been present as iodide. The thyroid counting-rate an hour and fifty minutes after the tracer then reflected the proportion of the dose which had been

TABLE II—RESULTS OF ^{131}I TESTS IN 10 SUBJECTS

Dose of iodopyrine (mg.)		60	30	10	10	10	10	5	5	5	5
Non-dischargeable ^{131}I in the thyroid after an hour and fifty minutes (% of dose)	Control	31	10	4	6	14	4	10	11	3	4
	Iodopyrine	1	0	2	0	1	2	5	8	2	2

Each subject was tested twice—after a single dose of iodopyrine by mouth, and without premedication. An hour after each tracer-dose of ^{131}I, 200 mg. potassium perchlorate was given by mouth. The ^{131}I uptake by the thyroid was recorded fifty minutes later (i.e., an hour and fifty minutes after the tracer-dose of ^{131}I).

organically bound. The results suggest that iodopyrine in single doses of 5–60 mg. inhibits the organic binding of iodine (table II).

A similar series of tests was performed in 9 other cases of non-toxic goitre, with and without single doses of 600 mg. phenazone. Phenazone had no significant effect on the proportion of organically bound ^{131}I after an hour and fifty minutes.

Discussion

3 adults developed goitres while taking felsol powders for asthma. The goitres became much smaller when felsol was replaced by a powder containing all its constituents except for iodopyrine. Goitre in asthmatic subjects receiving felsol has previously been described by Hydovitz and Rose (1956), Robbins (1956), and Maloof (1956). In the child recorded here a goitre was present at birth, the mother having taken felsol throughout pregnancy. These observations, though not conclusive, suggest that felsol can be a cause of goitre and that iodopyrine is the goitrogenic constituent.

Observations on case 2, and similar experiments in other subjects, showed that iodopyrine—but none of the other constituents of felsol—inhibits the organic binding of iodine. Since phenazone is not responsible, this effect of iodopyrine can be accounted for by the liberation of iodide soon after ingestion. Stanley (1949) and Childs et al. (1950) showed that the organic binding of iodine by the human thyroid is inhibited by single doses of iodide of the order of 1 mg. and upwards. The lowest dose of iodopyrine which has this effect (5 mg.) contains about 2 mg. iodine.

Long-continued ingestion of iodides occasionally causes goitre in man (Bell 1952, Morgans and Trotter 1953, Herbert and Petrie 1954, Turner and Howard 1956, Vanderlaan 1956, Rubinstein and Oliver 1957, Nixon 1957); but this happens to only a small minority of those who consume iodides regularly. Similarly, it seems that iodopyrine causes goitre in only a few of those who take it regularly. Ramsdell and Werner have also recorded goitres in newborn babies whose mothers had been taking large doses of iodide during pregnancy (Bell 1952). Work described by Brownstone and Pitt-Rivers (1959) in an accompanying paper strongly supports the view that the action of iodopyrine on the thyroid depends entirely on the iodide which is liberated from it.

Summary

3 adults developed goitres while taking felsol powders for asthma. The goitres became smaller when the patients were given the same powders without iodopyrine.

A baby whose mother was taking felsol during pregnancy had a goitre at birth. This later disappeared spontaneously.

Iodopyrine—but not the uniodinated parent substance, phenazone—inhibits the organic binding of iodine by the human thyroid.

The clinical evidence is compatible with the hypothesis that the effect of iodopyrine on the thyroid is wholly due to the iodide liberated shortly after ingestion.

Case 1 was under the care of Mr. D. Waterston and Dr. R. Bonham-Carter, case 3 under Mr. D. R. Davies, and case 4 under Mr. H. R. I. Wolfe and Dr. H. Nicholson. We are indebted to British Felsol Co. Ltd. for a supply of iodopyrine.

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"... An industrial metallurgist in the light-alloy field once told me, towards the end of the war, when every factory in England was preparing for the free-for-all it was assumed peace would bring, how his immediate boss, an accountant, dipt into the future, saw the vision of the world, and all the wonder that would be. 'All we need,' he assured my friend, 'is for you to produce an alloy combining the lightness of magnesium with the strength of steel, and we're there!' The accountant could not be persuaded of the impossibility of what he asked for. ... As much as politics, science is the art of the possible; but for non-scientists it is magic. At least, some sciences are magic. It would, for example, be very useful in some parts of the world to produce a breed of sheep which combined the succulence of lamb chops with the ferocity of tigers. They could fight their own wolves. But not even the most ignorant layman would ever seriously suggest the crossing of sheep and tigers. Perhaps if biology had become the model science, and not physics, the split in our culture ... would not have occurred."—WALTER ALLEN, *Encounter*, August, 1959, p. 67.

THE EFFECT OF IODOPYRINE ON THE THYROID GLAND OF THE RAT

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IODOPYRINE is the product of a reaction between phenazone or antipyrine (2 : 3-dimethyl-1-phenylpyrazol-5-one) and iodine. The preparation used * contained no free iodide, but the exact nature of the compound is unknown. Morgans and Trotter (see p. 374) have shown that iodopyrine depresses the uptake of ^{131}I by the human thyroid and its incorporation into organic linkage. In the present paper, the nature of the effect of iodopyrine on the rat thyroid is described.

Materials and Methods

Chronic experiments.—Groups of 12–24 male hooded rats weighing about 50 g. were fed on the Bruce and Parkes (1949) diet 41b (diet 41 without cod-liver oil and containing a vitamin supplement). The diets of the experimental animals contained iodopyrine to final concentrations of 0·1%, 0·02%, and 0·01%. Other groups of rats were fed the uniodinated precursor of iodopyrine, phenazone, in dietary concentrations of 0·6%, 0·3%, and 0·06%. The animals were weighed and their basal metabolic rates (B.M.R.) were determined at intervals during the two weeks of the experiment by the method of Tomich and Woollett (1954): they were then killed and their thyroids were removed, weighed, and examined for possible histological changes.

Acute experiments.—Groups of male hooded rats weighing 100 g. were given (*a*) 1·7 mg. iodopyrine orally in suspension in 0·1 ml. of a solution containing 1% tragacanth and 10% sucrose; (*b*) 1 mg. phenazone orally in a solution containing 10% sucrose; (*c*) 0·7 mg. iodide by intraperitoneal injection (equimolar doses). ^{131}I was injected intraperitoneally an hour before the animals were killed. The schedule of treatments is shown in the table. Thyroid analyses were done by the method

TREATMENT SCHEDULES

Number of rats	First treatment	Time after first treatment (hours)	^{131}I injected (μC)
4	1·7 mg. iodopyrine	1	20
4	1·7 mg. iodopyrine	6	10
4	1·7 mg. iodopyrine	16	5
3	1·7 mg. iodopyrine	23	2
4	0·7 mg. iodide	0·5	20
4	0·7 mg. iodide	5	10
3	0·7 mg. iodide	16	5
3	0·7 mg. iodide	23	2
3	1·0 mg. phenazone	1	2

of Pitt-Rivers, Galton, and Halmi (1958) to determine the relative amounts of organic and inorganic ^{131}I.

Results

Chronic experiments.—Both iodopyrine and phenazone appeared to have a toxic effect in all groups; they depressed growth by half or more except in animals receiving the lowest dose of phenazone. Several of the animals in both treated groups died before the end of the experiment and all seemed to be in very poor condition; they also showed a depressed B.M.R.

The thyroid glands of the treated animals in both groups did not differ in weight. Histologically the glands of iodopyrine-treated rats did not show any morphological difference from those found in normal rat thyroids.

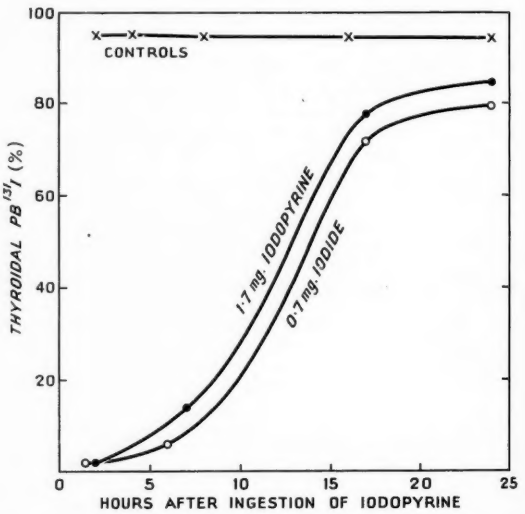
Acute experiments.—The results with iodopyrine and iodide are shown in the figure. In both groups of rats the incorporation of ^{131}I into organic linkage was at first inhibited, but the effect wore off. After twenty-four hours the protein-bound ^{131}I in the experimental groups approached the value found in the controls. Phenazone had no effect on the organic binding of ^{131}I.

* Supplied by British Felsol Ltd.

Comment

The present experiments have not demonstrated any goitrogenic effect of iodopyrine in the rat. The lowered B.M.R. of the treated animals was probably due to their poor condition rather than to hypothyroidism since the thyroid glands did not show any changes in weight or structure.

In 1948 Wolff and Chaikoff showed that the organic binding of iodine in the rat thyroid was suppressed by



Effect of iodopyrine and iodide in equimolecular doses on ^{131}I binding in the rat thyroid gland. The control values are taken from Galton and Pitt-Rivers (1959).

large doses of iodide, but the effect wore off after seventeen hours (Wolff et al. 1949). Galton and Pitt-Rivers (1959) have recently confirmed this and have further shown that the escape of the rat's thyroid gland from the iodide effect continues when iodide is fed in high doses for six or seven weeks.

The similarity between the effects of iodopyrine and an equivalent amount of iodide suggests that the only effect of iodopyrine on the thyroid is due to iodide. This is rapidly split off in the gut. The absence of any effect of iodopyrine on the thyroid after feeding it for two weeks can be explained by the findings of Galton and Pitt-Rivers (1959) that the normal rat thyroid is unaffected by prolonged iodide treatment. Finally, the complete lack of inhibition of thyroid function by 1 mg. phenazone (a dose molecularly equivalent to 1·7 mg. iodopyrine) at a time when the iodopyrine effect is strongest suggests that only the iodine in iodopyrine exerts any influence on the gland.

Summary

Iodopyrine and phenazone fed to young rats in various doses for two weeks have been shown to retard growth.

The toxic effect of these drugs is reflected in a lowered B.M.R., poor health, and deaths in both groups of treated animals.

Neither drug had any effect on the size of the thyroid and iodopyrine had no effect on its morphology.

Single doses of iodopyrine (but not of phenazone) prevented the incorporation of ^{131}I into organic compounds. This effect wore off at about the same rate as that of comparable doses of iodide.

These data suggest that the effects of iodopyrine on the thyroid can be accounted for if we suppose that the iodine in iodopyrine is released as iodide very soon after it is ingested.

We wish to thank Dr. Janet Niven for the histological examination of the thyroid glands.

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PHENINDIONE SENSITIVITY

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ALLERGIC reactions to phenindione ('Dindevan') are uncommon (see table) and usually present with fever, rashes, and agranulocytosis. Other reactions such as paralysis of accommodation (Calmettes et al. 1957). Christmas-factor deficiency (Sise et al. 1955) and steatorrhœa (Juel-Jensen 1959) have been reported.

Long-term anticoagulant treatment of patients with myocardial infarction is now common, and there is evidence that such treatment decreases the chance of a further coronary thrombosis (Toohey 1958, Medical Research Council 1959). Since dicoumarin derivatives are used for such long-term anticoagulation, more sensitivity reactions to them may be expected.

Two patients showing sensitivity to phenindione are described. In one of them phenindione therapy was resumed for a short time after the allergic reaction. In the other 'Warfarin' was successfully substituted.

Case-reports

Case 1.—A diabetic woman aged 50 had an anterior myocardial infarct on Aug. 13, 1956. She was treated with heparin for 24 hours and then with phenindione. In addition to phenindione, chlorpromazine was given from the 28th to the 57th day. On the 57th day she became febrile and felt unwell. All drugs were stopped. Next day her temperature reached 101·4°F and the white-cell count was 1600 per c.mm. (1% polymorphs). The platelet-count was 100,000 per c.mm.

Penicillin was started on the 58th day, and prednisone, 20 mg. daily, was given 2 days later. An allergic reaction to phenindione was considered probable. By the 63rd day numerous polymorphs had reappeared in the blood and the platelet-count was normal. Penicillin was discontinued and prednisone was gradually reduced, and stopped on the 72nd day.

Phenindione treatment was resumed on the 78th day without recurrence of fever. The polymorph-count, however, dropped from 5600 to the region of 800 per c.mm. over the next 18 days; and the platelet-count fell slightly. Phenindione was stopped on the 98th day and by the 117th day the polymorph-count was 4500.

The second fall in the white-cells count suggests a sensitivity reaction to phenindione rather than to chlorpromazine.

Case 2.—A man of 44 had an anterior myocardial infarct on April 2, 1955. After anticoagulation with heparin for 24 hours, phenindione was started. On the 25th day he was unwell and had a headache. Examination showed a temperature of 102°F and a few crepitations at the lung bases. There was no cough or sputum. The patient was started on penicillin; and, on the 30th day, phenindione was discontinued. The patient was afebrile by the 32nd day. His white-cell count was 8000 per c.mm. (polymorphs 5360, eosinophils 400) and the erythrocyte-sedimentation rate 65 mm. in one hour (Westergren, 200 mm. tube). Radiography showed slight restriction of movement of the left diaphragm.

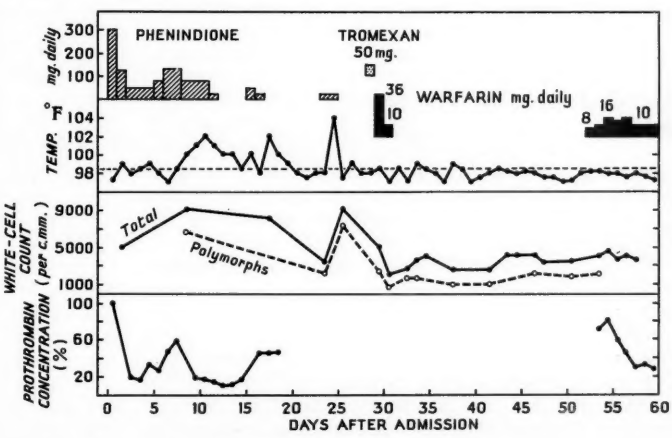
He remained well, apart from angina, until Oct. 11, 1958, when he had another infarct. Routine treatment, including anticoagulation with heparin for 24 hours and then with phenindione, was started. After a week the patient was very well, afebrile, with no abnormal physical signs, and a satisfactory prothrombin concentration.

On the 10th day he was unwell and febrile and had a headache. Hæmaturia on the 14th day (prothrombin concentration 10%) led to the stopping of phenindione; and next day he was afebrile. On the 17th and 18th day 50 and 25 mg. phenindione was given, and the fever (102°F), malaise, and headache returned. After a small hæmatemesis on the 18th day (prothrombin concentration 45%) the phenindione was stopped. He was afebrile and quite well by the 20th day. Headache was the most prominent symptom of this episode.

The pyrexia was investigated between the 14th and 20th day. Results were: hæmoglobin, 82%; white-cell count, 8200 per c.mm. (polymorphs, 6500); erythrocyte-sedimentation rate, 90 mm. in one hour (previously 32 mm.); urine, normal; blood-culture negative; extended Widal test negative; Paul-Bunnell test negative (Forssmann antibody titre 1/32); liver-function tests within normal limits; serum-proteins, 6·8 g. per 100 ml. (moderate increase in the α_2 and a slight increase in the γ globulins). The cerebrospinal fluid contained 12 lymphocytes per c.mm. but was otherwise normal. Radiography showed slight elevation of the left diaphragm.

The coincidence, on two occasions (see figure), of fever with the administration of phenindione suggested that the patient was allergic to this drug. The raised cell-count in the cerebrospinal fluid may be part of the allergic response.

On the 25th day when the patient was afebrile and off all drugs, 50 mg. phenindione was given. Within a few hours he had a rigor (temperature 104°F), headache, and malaise, confirming the sensitivity to phenindione. Intracutaneous skin tests to phenindione, ethyl biscoumacetate ('Tromexan'), and war-



Case 2: Clinical course of second infarct.

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CLINICAL AND PATHOLOGICAL FEATURES OF PHENINDIONE SENSITIVITY

No.	Reference	Day of onset	Symptoms *							Death	Prednisone
			Pyrexia	Rash	Low white-cell count	Hepatitis	Sore throat and mouth	Chest signs	Other symptoms		
1	Townsend et al. 1953	?	+	..	..	..	+	..	..	..	..
2	Brown and MacMillan 1954	25th	1	..	3	..	..	2 (râles)	(other drugs given)	..	..
3	Brown and MacMillan 1954	32nd	1	2	3	..	..	..	(other drugs given)	D	+
4	Kirkeby 1954	28th	2	1	5	4	3	..	6 (albuminuria)	D	+
5	Makous and Veer 1954	16th	1	2	3	4	..	..	(polyuria leukæmoid white-cell count)	..	+
6	Mayer 1954	24th	1	3	..	..	2	..	..	..	..
7	Pastor and Tetreault 1956	25th	1	3	4	..	..	2	..	..	+
8	Ager and Ingram 1957	27th	1	..	2	..	..	..	..	..	..
9	East and Beamish 1957	15th	2	1	..	3	..	..	4 (lukæmoid picture: tromexan used)	..	+
10	Johnman 1957	11th	1	2	5	..	4	3 (râles)	(tromexan used)	..	..
11	Burns and Desmond 1958	27th	1	2	3	4	5	..	Atypical mononuclears, immature polymorphs	D 2nd infarct	+
12	Case 1	58th	1	..	2	..	..	..	..	..	+
13	Case 2 (First episode)	25th	1	..	..	..	..	2 (râles)	..	..	..
	Case 2 (Second episode)	10th	1	..	3	..	..	2 (râles)	..	..	..

* Numbers indicate order of appearance of symptoms.

farin were negative and may account for the absence of a rash.

Prolonged anticoagulation was contemplated in this patient and 50 mg. ethyl biscoumacetate followed by 46 mg. warfarin were given between the 31st and 33rd days, without fever or malaise. On the 33rd day, however, the white-cell count was 2100 per c.mm. (polymorphs 850), and anticoagulants were discontinued. The white-cell count had risen to 4000 per c.mm. (polymorphs 2260) by the 53rd day and warfarin was recommenced at normal dosage. Satisfactory prothrombin concentration was obtained in a few days.

The patient was discharged from hospital on the 60th day; and he has been followed up clinically and with twice-weekly white-cell counts and prothrombin concentrations. Warfarin has so far been taken for 9 months without reaction.

Discussion

The findings in thirteen reported cases of phenindione sensitivity—excluding paralysis of accommodation, Christmas disease, factor-VII deficiency, and steatorrhœa—are shown in the table. The onset of the reaction is a little later than is usual in drug allergies. All the patients were febrile, and most felt ill with headache and general malaise. An erythematous, macular, confluent, scaling, and itchy rash has also been described.

Agranulocytosis has usually improved when phenindione has been discontinued and corticosteroids and antibiotics given. Agranulocytosis was associated with one death. Four severe reactions to phenindione have been associated with hepatitis. One of these patients died later from a renal lesion, possibly also part of the allergic reaction, and another died from a second myocardial infarct. Minor symptoms noted with phenindione sensitivity have included sore throat and ulcerative lesions of the mouth. Basal râles were found in four cases and led to a tentative diagnosis of bronchopneumonia in our second case.

Since sensitivity reaction to phenindione may be severe, immediate withdrawal of the drug is indicated at the first sign. In the first patient the use of corticosteroids, antibiotics, and discontinuation of phenindione led to rapid disappearance of fever and the return of the white-cell count and platelet-count to normal. This has been seen in other reported cases. Corticosteroids did not, however, prevent a further reaction when phenindione was recommenced after the steroids had been stopped.

The second patient showed that phenindione sensitivity may recur when the drug is given for a second time after an allergic reaction, even after an interval of 3 years. The patient showed a sensitivity to phenindione but not to warfarin. Ethyl biscoumacetate produced no immediate allergic response.

Johnman (1957) showed that a patient allergic to phenindione could be treated with ethyl biscoumacetate; but the period of treatment was not stated; and East and Beamish (1957) did not have the same experience.

If it is necessary to continue anticoagulation in a patient who develops a sensitivity to one of the dicoumarin drugs, the following scheme is suggested:

1. The dicoumarin derivative is discontinued.
2. If agranulocytosis occurs steroids and antibiotics are given.
3. The temperature, white-cell count, and any rash are observed carefully; and other signs of sensitivity (e.g., hepatitis) are looked for.
4. Further dicoumarin drugs are not given until the patient is afebrile and symptom-free, and has a normal white-cell count. Steroids should be discontinued before resuming anticoagulation, as they may mask a new allergic reaction which may emerge on stopping the steroids (Horne and Kay 1957).
5. Skin testing may show a positive reaction if the patient has shown a cutaneous sensitivity to the dicoumarin drug. With other drug sensitivities skin testing has occasionally caused agranulocytosis.
6. The temperature and white-cell count should be followed closely when the patient starts on the new anticoagulant. If a second sensitivity reaction occurs, it is likely to do so within one month.

Summary

Two patients with phenindione sensitivity are reported, one with two separate episodes.

The clinical and pathological findings of the reaction are described.

Treatment of such patients with other dicoumarin derivatives may be possible and a scheme of management is suggested.

We should like to thank Prof. M. L. Rosenheim for drawing our attention to case 1, which was under his care; and Dr. J. C. Hawksley under whom case 2 was admitted.

References at foot of next column

ALIMENTARY HISTOLOGY IN THE MALABSORPTION SYNDROME FOLLOWING PARTIAL GASTRECTOMY

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NUTRITIONAL disorders are not uncommon sequelæ of partial or subtotal gastrectomy. Loss of weight, usually associated with impairment of fat absorption is the commonest (Wollaeger et al. 1946, Lundh 1958); but a few patients develop the complete malabsorption syndrome with megaloblastic anæmia, hypoproteinæmia, and osteomalacia (Baird and Oleesky 1957).

Postgastrectomy malabsorption has been variously attributed to inadequate gastric or pancreatic function, defective secretion of bile, and mechanical factors such as intestinal hurry and incomplete mixing of food with bile and pancreatic juice (see review by Lundh 1958). None of these, however, is invariably present, nor has therapy based on any of them resulted in clinical improvement more than occasionally.

An obstacle to understanding has been the sparsity of histological studies. The disorder is rare and autolysis of the intestinal mucosa after death is rapid. After the early studies of Thaysen (1931) it was generally accepted that the small bowel presents no consistent histological abnormality in tropical sprue and, by inference, in the idiopathic malabsorption syndrome; but this conclusion was challenged by Paulley (1952, 1954). He described inflammation and atrophy of the jejunum in biopsy material from patients with "sprue", and his findings have been confirmed by other workers using peroral or operative intestinal biopsy (Doniach and Shiner 1957, Sakula and Shiner 1957, Butterworth and Perez-Santiago 1957, Bolt et al. 1958). It is becoming increasingly probable that idiopathic malabsorption syndrome without demonstrable changes in the intestinal mucosa is at best extremely uncommon.

The histological appearances in the upper alimentary tract following partial gastrectomy have been studied by several workers using peroral suction biopsy. Palmer (1954), Joske et al. (1955) and Lees and Grandjean (1958) found that inflammation of the gastric remnant was common but were uncertain about its clinical significance. Lees and Grandjean (1958) also reported that upper-jejunal biopsies were normal, despite gastritis in the proximal gastric remnant. The only report available to us dealing with alimentary histology in postgastrectomy steatorrhœa is that of Paulley et al. (1957). They found patchy jejunal atrophy in sections obtained by rapid post-mortem fixation of the gut in a man dying of intestinal malabsorption two years after a Polya gastrectomy.

The present paper reports 4 cases with proven intestinal malabsorption after gastrectomy.

DR. BINGLE AND DR. SHINE: REFERENCES

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Material and Methods

Our 4 patients had demonstrable absorptive defects after partial gastrectomy and in all of them histological material from the jejunum was available. In 1 patient gastric mucosa was also examined.

Absorption of *d*-xylose was estimated by the method of Benson et al. (1957). Fat-balance analyses were performed by the method of Frazer (1956): patients had a six-day period on a daily fat intake of at least 75 g.; and results were expressed as fæcal stearic-acid equivalent.

The concentration of vitamin B_{12} (cyanocobalamin) in the serum was determined by microbiological assay, using *Euglena gracilis* (Ross 1952). The absorption of orally administered radioactive vitamin B_{12} was tested by a urinary excretion method (Pitney and Stokes 1958) or a fæcal excretion test. This consisted in estimating fæcal radioactivity as a percentage of the orally administered dose of 1 μg. radioactive vitamin B_{12}. The normal range is still under investigation, but usually lies between 60% and 80%. When radioactive vitamin B_{12} was administered with oral intrinsic factor, the dose of the latter was 50 mg.* This amount has been shown to promote normal absorption from an oral dose of 0·6 to 1·0 μg. radioactive cyanocobalamin in patients suffering from pernicious anæmia.

Gastric and jejunal biopsy specimen were obtained either by the method of Wood et al. (1949) or at operation. Although 2 of the 4 patients eventually came to necropsy, it was not possible in either to secure early fixation by the introduction of formaldehyde into the abdomen. All specimens were fixed in formol saline and paraffin sections were prepared by standard methods.

Case-reports

Case 1.—A man aged 66 was admitted to the Royal Perth Hospital on Nov. 25, 1957, complaining of persistent diarrhœa with loss of weight during the previous eighteen months. He had undergone a partial gastrectomy for chronic duodenal ulcer in 1949 and cholecystectomy a year later. He remained well and fully employed until eighteen months before admission. He then noted the gradual onset of diarrhœa, with pale, loose, foul, frothy motions which floated on water. His bowel actions varied from five to eighteen daily. This diarrhœa was associated with flatulence and vague abdominal pains. His appetite was unimpaired, but he lost over 2 st. in weight.

Examination.—He was a wasted man, with dry, scaling, atrophic skin and pigmentation of the exposed parts. His tongue was not atrophic. His abdomen was slightly distended and doughy to palpation. The liver was enlarged to 2 cm. below the right costal margin. There was dependent œdema of both legs but no proteinuria.

Investigation.—He had gross steatorrhœa (table). The low serum-albumin suggested impaired protein absorption, but full nitrogen balances were not attempted.

X-rays showed an extensive Polya-type gastrectomy, with considerable reflux into the afferent loop. Follow-through showed a coarse mucosal pattern in the jejunum and segmentation of barium in the ileum. There was also a generalised osteoporosis without pseudofractures.

Course.—Treatment with rest in bed, steroids, and a gluten-free diet were ineffective. The Polya gastrectomy was then converted to a gastroduodenostomy; but he developed a burst abdomen on the tenth postoperative day and died about four weeks later.

Necropsy.—This was performed some twenty-four hours after death. Because of postmortem invasion by anærobic

* Lederle batch 186–1, supplied through the courtesy of Dr. L. Ellenbogen.

THE RESULTS OF LABORATORY INVESTIGATIONS IN 4 PATIENTS WITH POSTGASTRECTOMY INTESTINAL MALABSORPTION

Test	Normal value	Case 1	Case 2	Case 3	Case 4
Hæmoglobin	..	12·8	12·3	9·6	8·1
Mean corpuscular volume	75–100 cμ.	104	98	121	137
Bone-marrow	Normoblastic	Normoblastic	..	Megaloblastic	Megaloblastic
Serum-vitamin B_{12} concentration	Greater than 180 μμg. per ml.	580	497	34	46
Schilling test	16–36%	..	..	2·7 : 17·4*	..
Radioactive vitamin B_{12} absorption	Greater than 60% absorbed	43%	52%	..	20% : 78%*
ABO blood-group	..	O	O	A	O
Fæcal fat	Less than 25%	32	49	44	..
Fat-balance	Less than 5 g. per day as stearic acid	27·7	35·5	10·5	22·4
Serum-cholesterol	150–280 mg. per 100 ml.	95	178	278	200
Serum-carotene	Greater than 70 μg. per 100 ml.	..	27	47	30
Serum-albumin	3·5–5·5 g. per 100 ml.	1·2	1·9	3·7	2·8
Serum-globulin	1·5–3·5 g. per 100 ml.	2·5	3·7	3·2	4·5
Serum-calcium	9–11 g. per 100 ml.	7·9	9·5	11·6	9·1
Serum-phosphorus	3–5 g. per 100 ml.	4·4	2·4	3·3	3·0
Serum-iron	60–180 μg. per 100 ml.	60	60	55	24
Histamine test-meal	..	Free acid present	Achlorhydria	Achlorhydria	..
Serum-amylase	Less than 200 Somogyi units	135	55	..	440
Serum-alkaline-phosphatase	3–13 King-Armstrong units	13·5	44	8·9	11·4
d-xylose absorption	5-hour urine: 4·1–8·2 g.	5·5	6·6	3·8	5·4

* Test performed with oral intrinsic factor.

organisms detailed histological study of the alimentary tract was unrewarding. Despite his previous steatorrhœa, there was moderate atheroma of the aorta and cerebral arteries. The pancreas showed no evidence of chronic inflammation. The liver was histologically normal.

Biopsy findings.—Specimens were obtained on March 25 and May 16, 1958—only gastric mucosa on the first occasion, but both gastric and jejunal mucosa on the second. Both gastric biopsies showed severe atrophic gastritis, the mucosa being reduced to approximately half the normal width (fig. 1). The mucosal surface of the jejunum was irregular, and many of the villi were shorter and thicker than normal. The lamina propria contained an increased number of lymphocytes and plasma-cells (fig. 2). These appearances were considered to represent early atrophic jejunitis.

Case 2.—A man aged 50 was admitted to the Royal Perth Hospital on April 4, 1958. He had been known to have diabetes mellitus for twenty-two years and rheumatoid arthritis for seven years. Six months before admission a partial gastrectomy had been performed elsewhere for gastric ulcer. Operation had been followed by progressive loss of weight from 140 to 100 lb., and it was this which caused his referral to hospital. His only other symptoms were flatulent dyspepsia and painful stiffness of his joints.

Examination.—He was a wasted man with grey hair. He had slow auricular fibrillation. His skin was thin and atrophic, and his tongue red, smooth and fissured. He had advanced rheumatoid arthritis and pitting œdema of both feet and ankles.

Investigations.—Despite the absence of diarrhœa, he was found to have gross steatorrhœa and a serum-albumin of only 1·9 g. per 100 ml. (table). Liver-function tests suggested slight hepatic damage, but they were difficult to interpret, because of active rheumatoid disease and malabsorption.

X-ray examination.—The barium meal showed a slight corkscrew deformity of the œsophagus, a partial gastrectomy with gastrojejunal anastomosis, and segmentation and clumping of barium in jejunal and ileal loops. Very little barium entered the afferent loop, and the small-bowel transit-time was within normal limits.

Course.—A high-calorie, high-protein diet, with supplements of vitamins and folic acid, oral prednisolone, salicylates, and intensive physiotherapy produced a slow but steady symptomatic response and a slight gain in weight. After his discharge

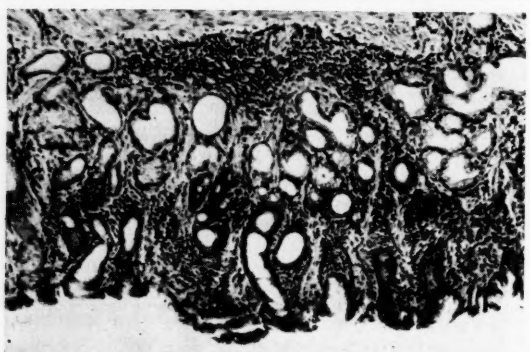

Fig. 1—Gastric mucosa in case 1, showing atrophic gastritis with inflammatory infiltration and glandular atrophy (hæmatoxylin and eosin, ×105).

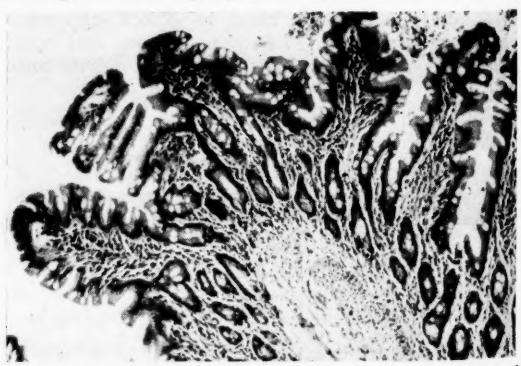

Fig. 2—Jejunal mucosa in case 1, showing slight broadening and deformity of the villi and some inflammatory infiltration (H. & E., ×105).

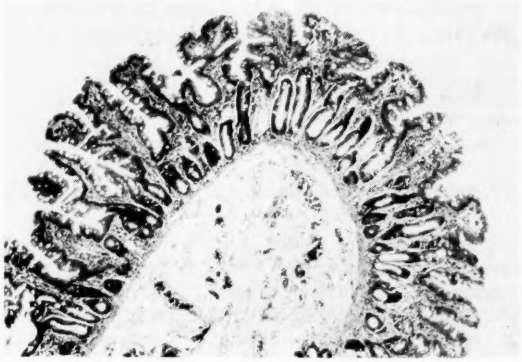

Fig. 3—The thickened and blunted villi in case 2 (H. & E., ×33).

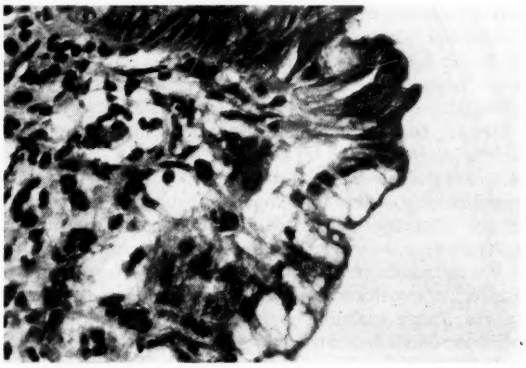

Fig. 4—Vacuolation of the columnar epithelium of the villi shown in fig. 3 (H. & E., ×420).

from hospital he was seen once in the outpatient clinic. He died elsewhere shortly afterwards.

Necropsy.—A limited postmortem examination showed the cause of death to be tuberculous bronchopneumonia. Autolysis prevented assessment of the intestinal mucosa. The pancreatic parenchyma showed no significant change. The liver showed mild cholangitis without evidence of biliary obstruction. There was no evidence of tuberculous enteritis.

Biopsy findings.—Jejunal biopsies were performed on June 6, and Aug. 7, 1958. In the first biopsy the mucosal outline was distorted, many of the villi being shortened, thickened, and blunted at their tip (fig. 3). Many of the epithelial cells showed cytoplasmic vacuolation (fig. 4). These vacuoles varied in position, being either supranuclear or subnuclear: they did not stain with the periodic-acid Schiff technique. The goblet-cells were increased. The lamina propria was slightly œdematous and contained a heavy inflammatory infiltrate of polymorphonuclear leucocytes, lymphocytes, and plasma-cells. In the second specimen the changes were even more pronounced, some villi being virtually obliterated.

Case 3.—A man aged 58 first developed rheumatoid arthritis in 1940. In 1946 parenteral gold therapy gave symptomatic relief. In September, 1953, he had a massive hæmatemesis for which a partial gastrectomy was performed. His weight was then 105 lb. He was again admitted to hospital in November, 1956, with acute gastroenteritis. He was slightly anæmic (Hb, 10·6 g. per 100 ml.); but his bone-marrow showed no megaloblastosis; and his response to oral iron was satisfactory. In December, 1957, he presented with recurrence of anæmia and weight-loss. He also complained of anorexia, frequent vomiting, mild diarrhœa (at least two bowel actions daily), soreness of the mouth and tongue, and a tendency to bruising.

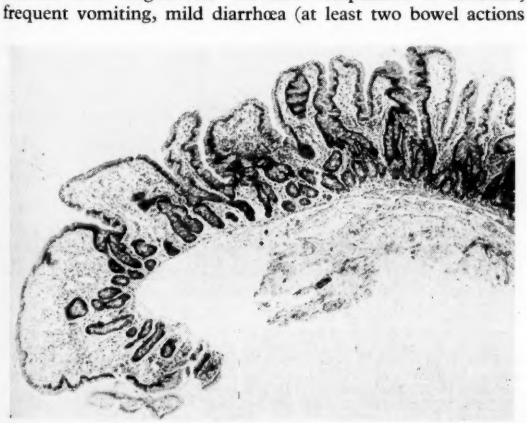

Fig. 5—Advanced atrophic jejunitis in case 3. Most of the villi are short and broad. The lamina propria is œdematous (H. & E., ×33).

Examination.—He was a grey-haired man with obvious recent weight-loss and advanced rheumatoid arthritis. No abdominal mass was palpable and there were no signs of peripheral neuritis. His weight was 91 lb.

Investigations.—He had a macrocytic megaloblastic anæmia and impaired fat and carbohydrate absorption (table).

X-ray examination.—Barium meal revealed a partial gastrectomy with gastrojejunostomy.

Progress.—Treatment with vitamin B_{12} produced a reticulocytosis and restored the blood picture to normal. He is continuing treatment with salicylates for his rheumatoid arthritis.

Biopsy findings.—Jejunal biopsy was performed twice—on Jan. 21, and Feb. 14, 1958. Both specimens showed marked atrophic jejunitis—blunted villi with short, broadened bases, and in some areas the absence of both villi and crypts. The lamina propria was œdematous and contained many dilated channels lined by endothelium. In the second biopsy there was also some cytoplasmic vacuolation with infiltration of the lamina propria by eosinophils, plasma-cells, and lymphocytes (fig. 5).

Case 4.—A woman aged 68 was first admitted to the Royal Perth Hospital on Sept. 23, 1958, for investigation of anæmia. Five years previously a subtotal gastrectomy had been performed elsewhere for multiple, benign gastric ulcers. After the operation, she had been well, though she had to take frequent small meals. Some months before admission she noted increasing tiredness, and she lost some 25 lb. weight. There had been no vomiting, diarrhœa, or overt blood-loss.

Examination.—She was a pale woman with grey hair. Her tongue was smooth and atrophic. The reflexes in her lower limbs were diminished and sensation was slightly impaired.

Investigations.—She had a macrocytic, megaloblastic anæmia and impaired fat absorption (table). The low serum-albumin suggested a defect in protein absorption.

X-ray examination.—The history of a subtotal gastrectomy with gastrojejunostomy was confirmed. The small bowel showed coarsening of the mucosal folds, segmentation and clumping of barium, and some dilated loops.

Progress.—Parenteral vitamin B_{12} produced a reticulocytosis of 20% and a rise in hæmoglobin concentration. Her subsequent progress has been satisfactory.

Biopsy findings.—Jejunal biopsies were obtained on Oct. 7, and Dec. 19, 1958. Neither specimen showed significant abnormality.

Discussion

The histological appearances in the jejunal specimens from the first 3 patients were, in general, similar to those reported in idiopathic steatorrhœa (Paulley 1954, Salvesen and Skogrand 1957, Butterworth and Perez-Santiago 1958). The abnormalities were, however, limited to the mucosal layer, and the inflammatory infiltration of the

submucosa described by Paulley (1954) and Salvesen and Skogrand (1957) was not seen in our cases. Gresham et al. (1958) and Himes and Aldersberg (1958) have described abundant granules of brown pigment within the muscle-fibres of the muscle layers and muscularis mucosæ in cases of sprue. In our material the muscle layers were present only in the operative biopsy specimen from case 1; and after careful search two fibres were found to contain granules of pale brown pigment. There was no pigment in the fibres of the muscularis mucosæ in any of the specimens.

We found atrophic jejunitis in 3 of our 4 cases of post-gastrectomy malabsorption, the changes being gross in 2. In the fourth patient changes in the biopsy specimens were minimal, but this does not necessarily mean that they were absent. Paulley et al. (1957) have reported a similar case in which patchy atrophic jejunitis was demonstrable at necropsy but not on biopsy. It should be noted, however, that in our patient the intestinal absorption of labelled vitamin B_{12} more closely resembled that found in pernicious anæmia than that in the malabsorption syndrome.

The similarity of the jejunal changes in postgastrectomy steatorrhœa and the changes described by other workers in the idiopathic malabsorption syndrome suggests a possible relationship between the two conditions. This may well have important clinical implications. It has been assumed that steatorrhœa following gastrectomy may be attributed to some mechanical or secretory malfunction produced by surgery. It is equally possible, however, that the role of surgery is merely to make manifest a previously present (if latent) defect in small-bowel function. There is in fact some clinical evidence of possible relation between peptic ulcer and the idiopathic malabsorption syndrome. The preponderance of blood-group O in patients with peptic ulcer (Billington 1956) is also found in patients with non-tropical sprue and in approximately the same proportions (Joske and Benson 1958). The ulcerogenic tumour of the islets of Langerhans described by Zollinger and Ellison (1955) results both in peptic ulceration and in intestinal malabsorption (Maynard and Point 1958).

Should this suggestion be substantiated, it may prove possible by preoperative screening-tests to diagnose patients who are especially liable to develop "post-gastrectomy steatorrhœa", and therapy can be planned accordingly. Further studies to elucidate this are in progress.

Summary

An investigation of 4 patients with intestinal malabsorption after partial gastrectomy with gastrojejunostomy showed atrophic jejunitis in 3.

The histological changes resembled those seen in the idiopathic malabsorption syndrome; and it is suggested that the two conditions may be related.

We wish to thank members of the honorary medical staff of the Royal Perth Hospital for permission to investigate patients under their care, and Dr. D. H. Curnow, Dr. W. R. Pitney, and their colleagues, for the laboratory investigations. The photomicrographs were prepared by Mr. H. Upeniecks of the University of Western Australia.

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SEPARATION OF FACTORS IN LUPUS ERYTHEMATOSUS SERUM REACTING WITH COMPONENTS OF CELL NUCLEI

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AFTER Hargraves' (1948) discovery of the L.E. cell, serological methods were used to demonstrate a reaction between the sera of patients with lupus erythematosus (L.E. sera) and (1) isolated cell nuclei (Miescher 1955), (2) desoxyribonucleic acid (D.N.A.) (Seligmann 1957, 1958), and (3) elements of cell nuclei other than D.N.A. (Robbins et al. 1957). Since a factor reacting with cell nuclei is found in certain sera which do not form L.E. cells (Friou 1958, Bardawil et al. 1958), and since in some L.E. sera removal of anti-D.N.A. activity with D.N.A. does not remove the L.E. cell factor (Deicher et al. 1959), separation of some of these multiple serum factors from the L.E. cell factor ought to be possible. In the present experiments, chromatographic fractionation of a L.E. serum on a diethylaminoethyl cellulose column served to separate the factor responsible for the production of L.E. cells from some of the other factors which react with components of cell nuclei.

Method

Serum (1·0 ml.) from a 34-year-old woman with systemic lupus erythematosus was fractionated by chromatography on a diethylaminoethyl cellulose column. The procedure, modified from that of Fahey et al. (1958), uses 150 ml. of pH 8·0 phosphate buffer; the serum is applied at 0·02 *M* phosphate concentration, and is eluted by progressively increasing the ionic strength of the eluting solution. The effluent from the chromatogram was divided into 10 pools and each pool was concentrated to an equal volume (1·0 ml.) by ultrafiltration, dialysed against pH 7·6 buffered saline, and tested as follows:

The tannic-acid-treated red-cell test (Boyden 1951) was used to detect the reaction with a human liver-nucleoprotein extract. The "tanned" red blood-cells were coated with a saline-diluted nucleoprotein-containing solution, made by aqueous extraction of a crude preparation of human liver-cell nuclei (Chargaff and Davidson 1955, Goodman and Bowser 1958).

Reactivity with nuclei of intact cells was determined by exposing frozen sections of mouse liver to the serum fractions. After washing with buffered saline (pH 7·4) to remove the portion of serum fraction not attached to the nuclei, fluorescein-labelled antibody to human gamma-globulin was applied to the section. Excess fluorescein-labelled anti-human gamma-

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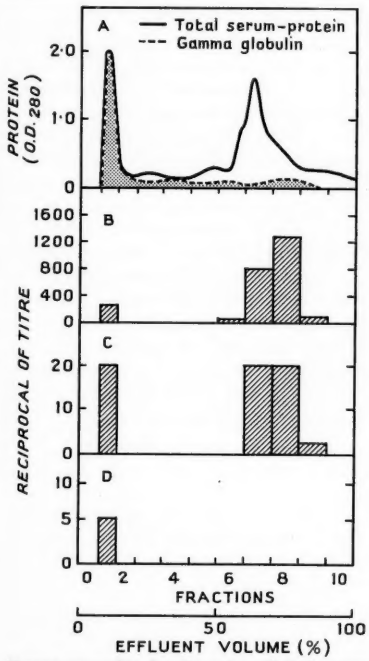

Chromatographic fractionation of L.E. serum with the results of testing the fractions for reactivity with components of cell nuclei.

globulin was removed by washing, and the section was examined under the ultraviolet microscope to determine whether gamma-globulin from the L.E. serum fraction had become localised to the cell nuclei (Holborow et al. 1957).

To determine the L.E. cell activity of each fraction, 0·2 ml. of the 1·0 ml. concentrated fraction was added to 1·0 ml. heparinised normal blood, the mixture was rotated with glass beads for thirty minutes at 37°C and, after centrifugation, a careful search was made for L.E. cells in the Giemsa-stained smears of the buffy coat.

Results

The results are summarised in the figure.

In part A, the distribution of the gamma-globulins (Fahey and Horbett 1959; not determined in this experiment) is illustrated by the shaded area under the total protein peaks. Below the graph of protein distribution are shown the activities of these fractions.

In part B is shown the reciprocal of the titre of reactivity with human liver-nucleoprotein extract. The reaction is with a heat-stable substance destroyed by incubation with desoxyribonuclease, presumably a nucleoprotein. The serum factors which react with human liver-nucleoprotein extracts, it should be noted, may not be the same as those which react with similar extracts made from calf thymus (Goodman 1959). The highest titres of reactivity were found in chromatographic effluent pools 7 and 8. In two other L.E. sera which reacted with this nucleoprotein extract, the activity was found entirely within the gamma-globulins when the sera were fractionated by zone (block) electrophoresis. When the separated gamma-globulins were fractionated chromatographically a distribution of activity similar to that illustrated here was obtained.

In part C is shown the reactivity with mouse liver-cell nuclei found in the test using fluorescein-labelled antibody to human gamma-globulin. Titres of 1 : 20 were found in effluent pool 1 and pools 7 and 8, while pool 9 was active only when tested undiluted.

As shown in part D, L.E.-cell factor was found only in fraction 1. When this fraction was tested at 1/5 dilution, large numbers of L.E. cells were produced, and even when tested at 1/10 dilution an occasional L.E. cell was seen, although the final titre was taken as 1/5. The original serum tested in the same way was considered positive at a dilution of 1/10. No suggestion of L.E.-cell activity was found in tests of the other fractions.

The serum was diluted 1/10 with 0·15 *M* NaCl solution and centrifuged at 38,000 r.p.m. for two and a half hours in the 40 rotor of the ' Spinco ' model L preparative centrifuge. Tests of eight fractions extending from the top to the bottom of the ultracentrifuge tube showed that the major portion of the factors reacting with human nucleoprotein had the sedimentation characteristics of the gamma-macroglobulins.

Discussion

These findings show that at least some of the factors found in L.E. sera which react with cell-nucleus components differ from the serum factor(s) responsible for the production of L.E. cells. All these serum factors are gamma-globulins. The factor responsible for production of L.E. cells has been shown to be a gamma-globulin with an ultracentrifuge sedimentation coefficient of about 7*S* (Holman and Kunkel 1957, Fallet et al. 1958), and the present observations are consistent with these findings since the fraction-1 proteins are entirely 6·6(7)*S* gamma-globulins (Fahey and Horbett 1959). Those gamma-globulins which appear in the effluent pools 7 and 8 (which corresponds to gamma-globulin fraction 5 of Fahey and Horbett 1959) are known to be largely gamma-macroglobulins (sedimentation coefficient = 18*S*) and this region constitutes the principal, if not the only, site of gamma-macroglobulin elution under these conditions of chromatography. Ultracentrifuge studies of this L.E. serum confirmed the chromatographic evidence that the major portion of the factor(s) reacting with human liver nucleo-protein extract is a gamma-macroglobulin.

Summary

Previous studies employing immunological techniques have shown that lupus erythematosus sera may contain several factors reacting with components of cell nuclei. The present report shows that these serum factors can be separated chromatographically into at least two distinct fractions. The evidence further suggests that certain antinuclei activities reside in the 6·6(7)*S* gamma-globulins, and others within the 18*S* gamma-macroglobulins.

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Preliminary Communications

EFFECT OF ANABOLIC STEROIDS ON NITROGEN EXCRETION IN ACUTE POLIOMYELITIS

THE muscle destruction in paralytic poliomyelitis is associated with large nitrogen losses, which can be followed by analysis of the urinary nitrogen.[1 2] Attempts have been made to reduce this protein catabolism by a high caloric intake, as well as administration of protein or protein hydrolysates. However, when this treatment was tested during the 1953 poliomyelitis epidemic in Stockholm,[3] it proved difficult to establish any effect of the serum-albumin or protein hydrolysate by means of chemical analyses. The treatment was nevertheless considered to be of some clinical value.

The anabolically active steroids seemed to offer considerably better possibilities both of influencing the nitrogen balance and of determining their effect objectively. This is because, during the acute stage of severe poliomyelitis, the course of nitrogen excretion is fairly characteristic,[1 2 4] thus permitting determination of the effect of nitrogen-sparing therapy. In a severe case, with rapidly progressing paralysis, the urinary excretion of nitrogen increases rapidly during the first few days, and then reaches a plateau during the second week after the onset of paralysis. The daily loss then diminishes fairly rapidly during one to two weeks, which is followed by a period of very slow decrease lasting for some months. Thus, when the more or less completely paralytic stage is reached, with maximum nitrogen excretion, no abrupt deviations from this typical course are seen, either in the form of individual variations with some regression of the paralysis, or as a result of therapy. Consequently, it is possible from a relatively early stage to calculate fairly accurately the subsequent course of nitrogen excretion.

We have tested anabolically active steroids in four cases of severe poliomyelitis in the acute stage. The results were uniform, and were supported by several treatment series in the subacute stage. We report here two illustrative cases, and compare them with a typical reference case in which no steroid therapy was given.

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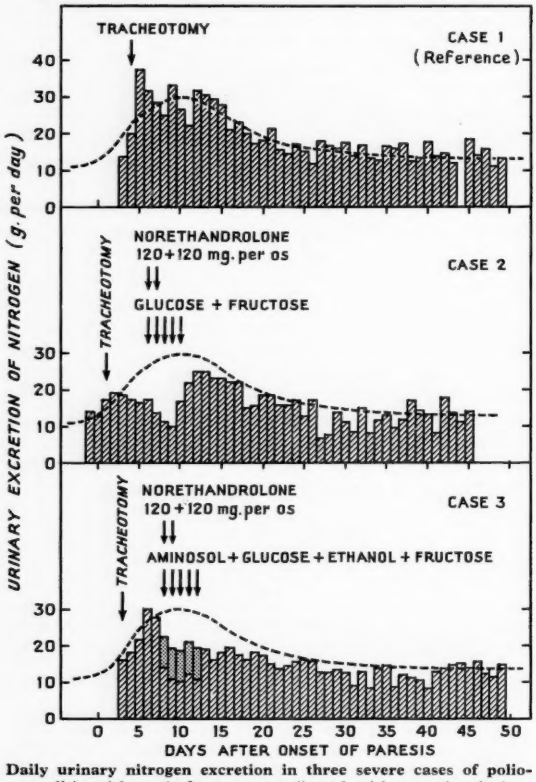

Daily urinary nitrogen excretion in three severe cases of poliomyelitis without (reference case 1) and with norethandrolone therapy (cases 2 and 3). The stippled sections in case 3 indicate the nitrogen supplied parenterally, which is deducted to obtain the nitrogen loss (hatched columns).

EXPERIMENTAL CONDITIONS

The three cases chosen to demonstrate the steroid effect were all of the same degree of severity (total paralysis of the extremities and respiratory paralysis). The patients were uniform with respect to age (22–23 years), body-weight (136–140 lb.), and sex (male). The onset was typical, and all had high fever and similar progression of the paralysis. The diagnosis was verified serologically. The patients had no hepatic or renal complications, nor did they show any other noteworthy clinical features. Respirator treatment was without complications.

As a short-acting anabolic steroid, we used norethandrolone ('Nilevar', 17-ethyl, 19-nortestosterone) which, given orally, has a rapid, transient effect.[5]

Case 1.—Reference case. Aged 22; body-weight 140 lb. No steroid therapy was given. During the first few days, 500–600 calories per twenty-four hours was administered parenterally, and thereafter a standardised diet in the quantity accepted by the patient.

Case 2.—Aged 22; body-weight 136 lb. During the first few days free diet. After that norethandrolone, 120 mg. per twenty-four hours in divided doses by mouth, was given for two days. Concurrently, and for a further three days, 1800 calories per twenty-four hours was administered parenterally, in the form of glucose and fructose.

Case 3.—Aged 23; body-weight 136 lb. The same treatment and the same dose of norethandrolone as in case 2. Concurrently, and for a further three days, 1800 calories per twenty-four hours parenterally, in the form of glucose, fructose, ethanol, and 'Aminosol' (a protein hydrolysate). The quantity of aminosol corresponded to 8·4 g. of nitrogen per twenty-four hours.

The urine was collected by catheter during the experimental period. The nitrogen loss through defæcation (enema) was disregarded. The total nitrogen was analysed by the micro-Kjeldahl technique.

RESULTS

The results can be inferred from the accompanying figure, showing the daily nitrogen loss which, in these cases, is the same as the total urinary nitrogen. Since in case 3 all nitrogen was supplied parenterally during the experimental period, this quantity (indicated by the stippled sections of the columns in the figure) has been subtracted from the total nitrogen to obtain the extent of the nitrogen loss (indicated by the hatched columns).

An average curve for the nitrogen loss during the acute stage has been plotted for the reference case (case 1); it is essentially typical of that in totally paralytic patients. For comparison, this reference curve (interrupted line) is also given in the figure for cases 2 and 3. In cases of poliomyelitis that are so alike with respect to severity, age, weight, and sex, the curve can be expected to conform closely with the course without steroid therapy.

Cases 2 and 3 show that oral administration of norethandrolone had a distinct nitrogen-sparing effect in the acute

5. McSwiney, R. R., Prunty, F. T. G. *J. Endocrin.* 1957, **16**, 28.

stage of poliomyelitis. We have not had enough severe cases to permit any definite quantitative comparison. It is however, remarkable that neither in these cases nor in our earlier trials could concurrent administration of a protein hydrolysate be observed to have any distinct nitrogen-sparing effect.

In the later stages of poliomyelitis, intramuscular injection of anabolic steroids—such as norethandrolone or 19-norandrostenolone phenylpropionate ('Durabolin')—produces only a tendency to a decreased nitrogen excretion, which is not sufficient to test the appropriate forms of therapy.

COMMENT

There is little doubt that the nitrogen loss in the acute stage of poliomyelitis can be decreased by administration of norethandrolone. Fairly good reproducibility can be obtained in testing these steroids in severe poliomyelitis, so conclusions can be drawn from relatively few cases. The mechanism underlying these catabolic processes evidently differs from that in such acute conditions as burns when norethandrolone has no effect,[6] and during the first postoperative days, when it also has no effect,[7] or a less pronounced one than during subsequent periods.

The implications of a nitrogen-sparing effect for muscle restitution remain to be seen. Possibly the milder cases, in which nervous function is relatively well restored, will benefit most from a decrease in the nitrogen loss during the acute stage.

We are indebted to the Swedish National Association against Poliomyelitis for financial aid.

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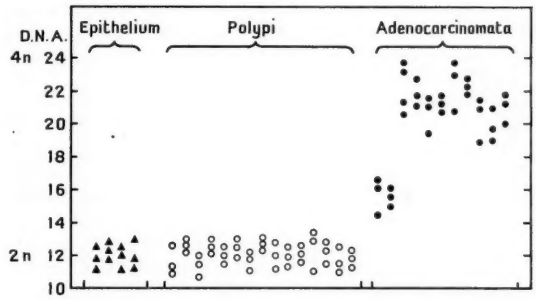
DESOXYRIBONUCLEIC ACID (D.N.A.) CONTENT OF HUMAN CARCINOMA CELLS

IN the histological diagnosis of neoplasia the pathologist is confronted with "borderline" lesions, in which the criteria of malignancy are only partly fulfilled and about which even experienced pathologists may differ. The criteria applied are largely subjective, and this has led us to search for more objective ones. In this investigation we have concentrated on neoplasms of the large bowel, among which diagnostic difficulties are not uncommon.

The method used has been the direct measurement of D.N.A. content of individual nuclei, using Feulgen-stained sections and the microspectrophotometric technique.

Material consisted of surgically excised tissues, fixed in 10% neutral formalin, embedded in paraffin, and sectioned at 10 μ. Sections were hydrolysed with N HCl for 60 min. at 60°C, stained in leucobasic fuchsin for 90 min., washed in water containing sulphur dioxide, and mounted in 'Technicon'.

D.N.A. content of individual cells was measured by the two-wavelength technique of Patau,[9] with the correction tables of Swift and Rasch.[10] All nuclei of benign and malignant epithelial cells were measured in metaphase and telophase, to eliminate variations due to synthesis of D.N.A. in interphase. As an additional check, measurements were also made on lymphocytes, in which mitosis and D.N.A. synthesis do not normally occur.



In the initial series, D.N.A. determinations were made on epithelial cells from 8 specimens of normal large-intestinal mucosa, on 29 histologically benign large-intestinal polypi, and on 23 large-intestinal adenocarcinomas. D.N.A. values of 30 epithelial nuclei were measured in each of these specimens. On our arbitrary scale lymphocytes gave a D.N.A. value of 6 units. Normal large-intestinal epithelial cells, and cells from histologically benign polypi, gave a D.N.A. value of 12 which corresponded to the expected doubling of chromosomal material during mitosis. No exceptions to these findings were discovered.

Carcinoma cells gave abnormal D.N.A. values, which did not correspond to those of normal epithelial cells or to whole multiples thereof. These abnormal values fell into two main groups, one centred on the D.N.A. value of 16 units, and the other on 21 units. Occasional normal values of 12 were observed, but these were probably due to the inclusion of some non-malignant epithelial or connective-tissue cells in mitosis. No abnormal values were found in the epithelium of normal bowel or histologically benign polypi. In a single carcinoma most of the cells gave a value of one of the abnormal numbers, 16 or 21, but occasionally readings were more equally distributed between the two abnormal values. Occasional carcinoma cells gave readings corresponding to whole multiples of the abnormal numbers. No correlation was demonstrated between the histological grade of malignancy of a carcinoma and its nuclear D.N.A. value.

These findings were confirmed in a small series of gastric lesions—normal mucosa, polypi, and adenocarcinomas. Carcinomas of the female breast and bronchus have also been shown to give abnormal nuclear D.N.A. values. Because of the clarity of these results, a second series of large-intestinal lesions was investigated in which the D.N.A. content of only three nuclei per tumour was measured. The values for 4 specimens of normal large-intestinal epithelium, 15 histologically benign polypi, and 11 adenocarcinomas are set out in the figure, and correspond exactly with those of the first series in which thirty nuclei per tumour were measured.

The results indicate that it may be possible to distinguish between benign and malignant tumours of some tissues by a small series of nuclear measurements. Such a method might well prove a valuable additional diagnostic tool in pathology. The results are reinforced by the similar findings reported by Atkin and Richards.[11] No histologically benign tissues were found to possess the abnormal nuclear D.N.A. values of the carcinoma cells; moreover it may prove possible to utilise D.N.A. measurements made in interphase also, since it seems likely that any cell is malignant which shows a D.N.A. value in interphase significantly greater than that of a normal cell in mitosis.

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In experimental tumours the D.N.A. value of the nucleus has been correlated and equated with chromosome number, and the possession of abnormal chromosome complements by malignant cells. In one adenocarcinoma of the large intestine of our series direct chromosome-counts were performed on fresh material obtained at operation, and gave a chromosome number identical to that calculated from the measured D.N.A. value. This aspect of the investigation and its theoretical implications are being studied and will be reported later.

A summary of this work was presented at the annual meeting of the American Association for Cancer Research last April.[12]

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"NOT POLIOMYELITIS"

THE remarkably low figures for poliomyelitis notifications this year are consistent with the results of routine tests at the Virus Laboratory, Ruchill Hospital, which serves roughly the West of Scotland. Whereas during the months of July and August, 1958, stool specimens for virus isolation were received from 89 cases with the clinical diagnosis of aseptic meningitis and 85 of paralytic poliomyelitis, during the same period of 1959 specimens were received from 96 cases of aseptic meningitis and from only 10 of paralytic disease. During these two months of 1958, isolations of 130 type-1 and 2 type-2 polioviruses were reported and no other enteroviruses were isolated. In the corresponding period this year not one poliovirus was isolated by the same methods of inoculation of monkey-kidney tissue cultures, but from a small proportion of stools a variety of Coxsackie (types A9, B2, B5) and ECHO (types 6 and 11) viruses were isolated. Agents producing paralysis and myositis typical of Coxsackie group-A viruses were isolated from 4 of 5 of this year's specimens, negative in tissue culture, tested by inoculation into suckling mice.

A preliminary analysis has been made of the clinical features of 30 cases of aseptic meningitis seen in Ruchill Hospital this year. The term "aseptic meningitis" includes cases with muscle weakness from which no poliovirus was isolated. Headache and vomiting predominated in an illness with rather vague symptoms at onset. Symptoms might remit before a sharp increase in headache and vomiting, and in some cases complaint of muscle weakness, resulted in admission to hospital. Meningeal signs were usually present and lumbar puncture showed abnormality of cerebrospinal fluid—mainly increase of cells without much change in protein content. In 20 cases the temperature was moderately raised on admission, but in most of them it had dropped to normal within forty-eight hours. Apart from continuance of vomiting for several days in a few instances, and, in others, the first appearance of vomiting some forty-eight hours after admission, progress in the majority was rapid and uneventful. Muscle weakness affected limbs in 8 cases (1 with respiratory involvement), respiration in 2 additional cases, palate in 1 case, and the facial nerve in 1 case. 6 patients required physiotherapy in an orthopædic unit because of residual weakness of limb muscles. There were no deaths. Epidemiological investigations have failed to show a common factor, though the majority of patients were children of 5–15 years and the peak of incidence of cases so far seen was in June.

Taken alone, the clinical observations might suggest an unusually mild outbreak of poliomyelitis, conceivably modified by widespread immunisation. The laboratory findings, however, indicate the absence of poliomyelitis virus from the community and the prevalence of various other potentially neurotropic enteroviruses including strains of group-A Coxsackie viruses which are non-pathogenic for tissue cultures and require inoculation of suckling mice for their identification. This preliminary communication is made in order to draw the attention of others to an interesting epidemiological situation while the outbreak is still in progress.

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Reviews of Books

Modern Science and the Human Fertility Problem

RICHARD L. MEIER, PH.D. New York: John Wiley. London: Chapman & Hall. 1959. Pp. 263. 48*s*.

THIS book is, in its general intention, a modern re-creation of Malthus—an attempt, that is, at social prediction based on the present patterns of fertility and population increase and the immediate likelihood of an effective and adequate means of controlling fertility. Dr. Meier's main contention—that such a means is within our reach if we have sufficient interest in finding it, and that it will in any case arrive within a few years—would probably be accepted by most human biologists, with the reservation that the end-results of a "contraceptive pill" which acts by upsetting ovulation have yet to be seen. A transient inhibitor of spermatogenesis may perhaps offer fewer risks of adverse side-effects.

In social prediction reiteration may be necessary, and if Meier sometimes reiterates the obvious he also gives disturbing examples of the effects of overfertility. In Mauritius, he claims, there are signs of the division of society into a self-supporting segment living normally, and a State-supported and pauperised segment living in camps which already tend to be custodial. This trend exists elsewhere, and implies, as Meier says, the effective life imprisonment of people whose only fault has been to be born at the wrong time and in the wrong place. His second social example is that of Puerto Rico, which is the current testing-ground for much American research on oral fertility control.

In considering the future, Meier discusses whether fertility control will develop rapidly enough to prevent still more serious problems, whether compromise will be reached with religious dogmas which oppose it, and the rate at which the price of suitable pharmaceuticals will decline. But he does not touch the fascinating, if less urgent, question of the probable influence of a reliable and simple contraceptive on sexual behaviour and attitudes. His book is in general humane in its approach, free from the excesses of pessimism and optimism which the subject usually provokes, and imbued with its extreme urgency. His survey of modern research on pandemic pharmaceuticals and of experience in field-testing is a useful source of references.

The Pathology and Management of Portal Hypertension

R. MILNES WALKER, M.S., F.R.C.S., professor of surgery, University of Bristol. London: Edward Arnold. 1959. Pp. 113. 35*s*.

Bleeding Esophageal Varices: Portal Hypertension

HIRSCH ROBERT LIEBOWITZ, B.S., M.D., assistant professor of clinical medicine, New York University College of Medicine. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959. Pp. 986. 183*s*. 6*d*.

WHAT a neat contrast these two books offer. Prof. Milnes Walker is succinct and provides just what an intelligent ignoramus needs to know. His monograph is easily read; no time is wasted and by the end the subject is in the reader's grasp. He has achieved his purpose of providing a guide to clinicians who may have to treat these patients. Dr. Liebowitz's approach is more monumental. Any experiment which touches even the smallest facet of the subject is mentioned; no relevant investigation remains unnoted, so that the reader is left with little doubt that all that is to be known can be found in the pages of this book.

The two works are complementary, and the man who wishes to pursue matters further after being stimulated by the monograph can turn to the tome. In short, Prof. Milnes Walker gives the brief word, Dr. Liebowitz the last word.

Automatic Ventilation of the Lungs

WILLIAM W. MUSHIN, M.A., M.B., F.F.A.R.C.S., professor of anæsthetics, Welsh National School of Medicine, University of Wales; L. RENDELL-BAKER, M.B., F.F.A.R.C.S., assistant professor of anæsthesia, Western Reserve University School of Medicine, Cleveland, Ohio; PETER W. THOMPSON, B.A., M.B., F.F.A.R.C.S., consultant anæsthetist, United Cardiff Hospitals and Welsh Regional Hospital Board. Oxford: Blackwell Scientific Publications. 1959. Pp. 349. 47*s*. 6*d*.

THE widespread practice of artificial ventilation of the lungs in anæsthesia and other branches of medicine when normal respiration starts to fail has prompted the design and production of automatic machines as substitutes for manual methods. This review of the subject and of the intricacies of automatic ventilators and of their accessories is, therefore, timely. But, as Professor Mushin and his colleagues note, it is not more ventilators that we need, but more understanding of those we have and of their clinical use. Unfortunately so many have already been introduced to clinical practice that most of the book, of necessity, consists of a somewhat dull catalogue describing each—56 in all—and its functional analysis in detail. The descriptions are well supplemented by illustrations and circuit diagrams when necessary. Automatic methods of ventilation, such as the tank or cuirass, that work by the application of pressure otherwise than through the trachea are not included. The introductory chapters on the physiological and clinical aspects of controlled respiration are useful and objective, and W. W. Mapleson contributes two chapters on the physical aspects of automatic ventilators.

The Degenerative Back and its Differential Diagnosis

P. R. M. J. HANRAETS, M.D., neurosurgeon, St. Ursula Clinic, Wassenarr, The Netherlands. Amsterdam and London: Elsevier Publishing Company. 1959. Pp. 690. 105*s*.

Dr. Hanraets has been particularly interested in the pathogenesis of low-back pain for over fifteen years, and he now draws on experience based on over two thousand laminectomies—including 700 operations on herniated discs, in the course of which, he notes in a whimsical aside, over 11 lb. of disc material was excised. Intervertebral-disc protrusions, he suggests, have too often been regarded as strictly localised lesions. He shows that usually they are manifestations of a widespread degenerative process affecting not only all the spine but often the whole patient, including his psychological reactions. The determining factors in this process include congenital anomalies, injury, and an inherited diathesis; and the ensuing syndrome of lumbago and sciatica may be due not only to disc herniation but to various lesions affecting the lumbosacral nerve-roots in the distal two-thirds of their course between the dural sac and root ganglion. The author's views will command wide respect in view of his great experience, his clear exposition, and a convincing series of beautiful illustrations. The section on the conservative and surgical treatment of back pain is particularly valuable, and here the most notable difference between his practice and that prevailing in this country lies in his advocacy of local anæsthesia for the great majority of laminectomies. Of the many works on spinal disorders few can be more comprehensive, painstaking, and stimulating than this. Its translator, Miss M. E. Hollander, deserves thanks for her competent and fluid rendering of highly technical material.

The Plasma Proteins

Clinical Significance. PAUL G. WEIL, B.A., M.D., M.SC., PH.D., director of transfusion service and assistant physician, Royal Victoria Hospital, Montreal, lecturer in medicine, McGill University. Philadelphia and Montreal: J. B. Lippincott. London: Pitman Medical Publishing Co. 1959. Pp. 133. 28*s*.

THIS little volume, one of a series of " Practitioner's Pocket Books ", sets out to survey the nature of plasma-proteins, methods of investigation, and the changes in pathological states. This is no mean programme, and considerable compression has been necessary. Dr. Weil gives no text references, but provides a short bibliography of important articles. Much of the information is set down without critical assessment, and accordingly, though the book will be intelligible to an informed reader, the practitioner to whom it is addressed may find it heavy going. Dr. Weil apparently accepts without qualification the pine-tree-pollen theory of the ætiology of sarcoidosis, the explanation of multiple sclerosis as an autoimmune disease caused by choroid-plexus secretion, and the necessity of giving fresh-blood transfusions for all coagulation disorders. Speculation is mixed with established fact, but an astonishing amount of current information is included.

Hunger and Food (London: World Federation of Scientific Workers. 1959. Pp. 123. 10*s*.).—The authors of these 12 essays come from Western Europe, Eastern Europe, China, Latin America, and North America; and the editor, Prof. Josué de Castro, is a former chairman of the executive council of the Food and Agriculture Organisation of the United Nations. Most of the essays discuss some aspect of the Malthusian dilemma and on the whole they strike an optimistic note. Advances in technical knowledge, if applied scientifically to agriculture, can produce the extra food needed to feed the world population, which has grown because of the conquest of the great infectious diseases. The Russian contribution states that the energy provided by photosynthesis enables the synthesis of 180 tons of organic substances per head of population annually. The problem is to make the links between highly productive plants and man as short and effective as possible. This can be achieved " by common, friendly and co-ordinated efforts to wrest from nature what she offers man in sufficient quantities ". The book can be recommended as a sensible and well-documented account of what world agriculture could achieve, provided the energies of mankind are not wasted on futile wars.

A Text Book of Medicine (10th ed. Philadelphia and London: W. B. Saunders. 1959. Pp. 1754. 115*s*. 6*d*.).—It is a pleasure to welcome the latest edition of this famous textbook, edited by Prof. Russell L. Cecil and Prof. Robert F. Loeb. There are a number of new articles on virus infections, industrial illnesses, and disorders of metabolism; and the section on neurology is strengthened by an account of cervical spondylosis written by Sir Russell Brain. The index is excellent, and a few key references are included with every article. A noteworthy feature is a new foreword by Prof. Dana L. Atchley on Physician Patient Communication. This rather cumbersome title heads a profound and pithy article on the art of good doctoring which sets the tone of what is not so much a reference book as a guide to the whole practice of medicine. This edition cannot fail to enhance the reputation of a work which has been highly regarded for over thirty years.

New Inventions

DEVICE FOR TIMING CINEANGIOCARDIOGRAMS USING THE ELECTROCARDIOGRAM

WITH the increasing use of high-speed cineangiocardiography in the investigation of congenital and acquired heart-disease, it has become necessary to time events during the passage of contrast media through the heart. Prinzmetal et al.[1] used the electrocardiogram (E.C.G.) displayed on a long-persistence oscilloscope and photographically incorporated into the cine frame, but this method could not be easily adapted to our equipment. Watson et al.[2] modified the method originally described by Lind et al.[3] for automatically marking the time of each cine exposure on a synchronous E.C.G. This ingenious method enabled the time relationship of each exposure to be determined, but, although precise, it required tedious counting of frames and continual reference to the E.C.G. We have found it more convenient to have a marker on each frame of the film. It is then possible to time frames during both systole and diastole irrespective of the camera speed or the heart-rate.

The Marker

The cineangiocardiograms were taken at a speed of 32–48 frames a second using a 35 mm. 'Arriflex' camera mounted on a standard 5 in. Philips image intensifier. A Philips DCX generator supplied a smoothed current to the undercouch tube.

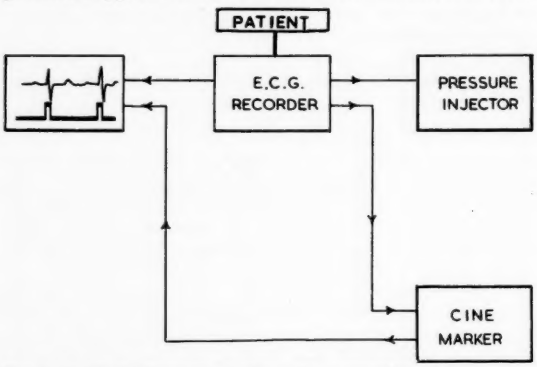

Fig. 1—A block diagram to show the connections between the electrocardiograph, the cine marker, and the timed pressure injector.

The marking device was part of an electronic unit, which was triggered by the R wave of the E.C.G. (fig. 1). The marker (fig. 2) consisted of a modified type-600 relay. A brass rod 30 mm. long and 1 mm. in diameter was mounted on the top of the armature in place of the residual stud. The relay contact assembly consisted of two changeover contacts, one of which was used to indicate electrically the movement of the brass rod on the multichannel photographic recorder. The marker was mounted on a plate of 'Perspex' with the rod above a fixed brass ring. The whole assembly could be conveniently positioned in the cassette-holder just below the image intensifier. The movement of the time marker, the duration of the injection of contrast medium, and the E.C.G. were all recorded simultaneously. A second unit, also triggered by the R wave, was used to activate a solenoid controlling a simple mechanical injector (fig. 1). The delay between the R wave and the injection of the contrast medium could be varied electronically. A unit of this type was recently used successfully for coronary angiography by Richards and Thal.[4]

Fig. 2—The cine marker mounted on a small plate of 'Perspex', showing the relay mechanism, the brass rod, and the brass circle.

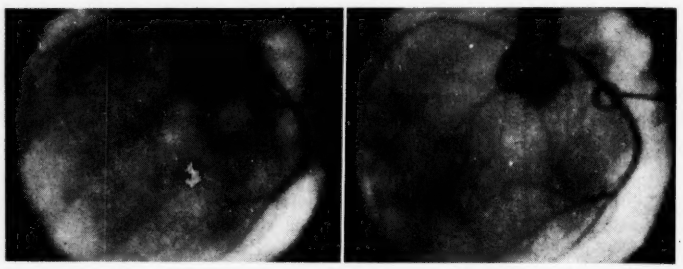

Fig. 3—Two frames from a coronary cineangiogram in a dog, to show (left) the marker in its zero position and (right) the marker when it has been triggered by the R wave of the electrocardiogram.

A monocular viewer attached to the cine camera enabled the radiologist to see through the shutter of the camera to position the cine marker before the injection of contrast medium was begun. The lever on the marker was arranged to move towards the top of the frame when triggered by the R wave of the E.C.G. The duration of the upward movement of the marker could be easily varied to suit the heart-rate.

The cine marker was first used experimentally during coronary angiographic studies in dogs (fig. 3). It was then used routinely in the timing of events in right and left heart cineangiograms and it was found to help considerably in their interpretation. The response of the time marker was sufficient for following rapid ventricular ectopic beats which occurred during selective injection into the right ventricle (fig. 4).

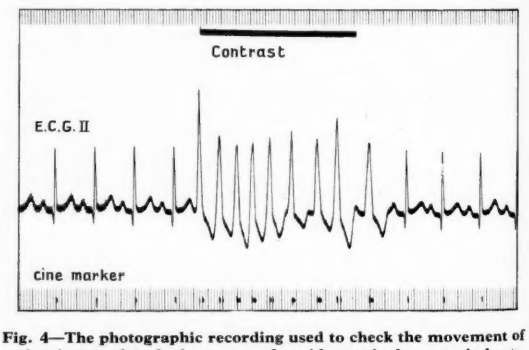

Fig. 4—The photographic recording used to check the movement of the cine marker during a run of rapid ventricular ectopic beats, following selective injection of contrast medium into the right ventricle.

When patients with aortic-valve disease are studied by cine-aortography it is possible to correlate the movement of the valve leaflets with the cardiac cycle and to time any reflux of contrast medium from the aorta to the left ventricle.

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1. Prinzmetal, M., Kennamer, R., Weiner, S. M., Bishop, J. R. *J. Amer. med. Ass.* 1956, **161**, 1229.
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3. Lind, J., Wegelius, C., Lichtenstein, H. *Circulation*, 1954, **10**, 195.
4. Richards, L. S., Thal, A. P. *Surg. Gynec. Obstet.* 1958, **107**, 739.

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LONDON 19 SEPTEMBER 1959

How Many Mouths?

"AND God blessed Noah and his Sons and said unto them Be fruitful and multiply and replenish the earth." At the time of the Deluge such advice was necessary, and when the Israelites received the same advice the world population was probably only 40 million. By the time of the first Elizabeth it had increased tenfold, but was still far short of the thousand-million mark when, at the close of the 18th century and on the threshold of the Industrial Revolution, THOMAS MALTHUS expressed an economist's concern at the alarming growth of population. Though the calculations which caused his gloom may have been faulty, there is no reason to doubt the general principle that food resources increase in arithmetical progression while population increases geometrically. During the next century food resources increased faster than he expected, and the prosperity of the Western world provided ample argument for his opponents, who were mostly more concerned with the ethical problems presented by birth control—though birth control as understood nowadays did not figure prominently among the remedies MALTHUS recommended.

According to Dr. HARRISON MATTHEWS [1] world population increased by 47 million last year; it will have doubled by the end of the century; and a thousand years from now, if the present rate of increase is maintained, there will be one person for every square yard of the Earth's surface. Food production increases at little more than 1% per annum, with prospect (Dr. MATTHEWS says) of a diminution in the rate of increase: population increases by more than 1·5% per annum, with every reason to expect increase in the rate. According to W.H.O.[2] 1800 million people are even now insufficiently nourished, and a P.E.P. report [3] suggests that the standard of living of underdeveloped countries cannot be raised or even maintained unless the rate of births is controlled. Ceylon is one example of the problem. The death-rate has fallen in the past seven years from 22 to 12 per 1000 (in Britain in the last century a similar fall took seventy years). The birth-rate, which is still increasing, is now 27 per 1000 per annum; and, even without further increase in the ratio, the population will double in thirty years. Population is increasing each year at the rate of 1 million in Japan, 5 million in India, and probably 10 million in China. India's twelfth anniversary took place in an atmosphere of gloom, for food prices are high and despite a bumper crop there is anxiety about her annual 2% increase in population. Mr. NEHRU has said [4] that "within seven years they would feed 460 million people, but that he did not quite see how". JULIAN HUXLEY [2] has remarked that, if the increase continues, man will become the cancer of the planet.

If we are to prevent famine we shall have to increase food-supplies or reduce fertility. Much more food could be provided for the countries which need it most if distribution were improved, waste were avoided, existing sources (such as the sea [5]) were more fully tapped, and new sources and new methods were exploited.[6] (Only last week a method of extracting edible protein—at least 90% pure—from vegetable matter, including grass and leaves, was announced in London.[7]) Such action could be taken only at a cost in money and effort that Governments are at present unwilling to bear; and whether in the long run even the most vigorous endeavour to increase food production could keep pace with the growth in world population is still disputed. Similarly, an effective means of limiting conception should not be beyond man's ingenuity, but there are many difficulties. Mechanical and chemical appliances are unacceptable to many, on ethical or religious grounds, and are not used effectively by the uneducated—though in India some progress has been made in this direction. The use of the "safe period" is acceptable to almost all, but is unreliable. Supposing the "safe period" could be made calculable, or, better still, extended pharmacologically, would it still be acceptable?

An oral contraceptive has long been sought, which would remove the act of prevention one step further from the act of consummation and thus suppress the guilt which still lingers in the minds of some who adopt contraceptive measures immediately related to intromission. There is irony in the fact that the widespread interest of the past twenty years in the limited and personal problems of infertility may have led, through research into the steroid compounds concerned in sex physiology, to the discovery of an oral contraceptive. Experiments in animals, and observations in man for medical reasons not associated with contraception,[8] have given evidence of the probable efficacy and relative safety of certain of the steroids in inhibiting ovulation without suppressing regular menstruation. The first large study of their use for this purpose in women has now been reported by PINCUS and others.[9]

The suitability of a contraceptive is measured by its acceptability, its efficacy, and its safety. Acceptability of the steroids—lack of an inherent antipathy to their use as contraceptives—seems to be exceedingly high. In this trial (conducted in Haiti and Puerto Rico) the causes of women withdrawing from the experiment seem to have been related to psychogenic reactions or lack of interest, both of which could be countered by explanation and encouragement. The efficacy of the steroids is also high, provided that the method is applied

1. British Association, Annual Meeting, York, 1959.
2. The Human Sum (edited by C. H. Rolph). London, 1957.
3. P.E.P. Report. World Population and Resources. London, 1955.
4. *Manchester Guardian*, Aug. 15, 1959.
5. See *Lancet*, 1954, ii, 1186.
6. *ibid.* 1958, i, 575.
7. *Times*, Sept. 11, 1959.
8. Rock, J., Garcia, C. R., Pincus, G. Laurentian Hormone Conference, September, 1956.
9. Pincus, G., Garcia, C. R., Rock, J., Paniagua, M., Pendleton, A., Laraque, F., Nicolas, R., Borno, R., Pean, V. *Science*, 1959, **130**, 81.

thoroughly. There remains the question of harmful effects. Can ovulation be inhibited indefinitely without irrevocable damage to the genital tract? No-one yet knows the answer, though CROSSON[10] has reported studies, now nearing the end of their third year, in which laparotomy demonstrated normal ovarian tissue, and in PINCUS' series fertility seemed to be unimpaired when the oral contraceptive was discontinued. Another possible risk is of malignant disease, for the steroids have long been regarded as ultimately carcinogenic. Yet a further possibility (not mentioned by PINCUS) is that inhibition of ovulation, even when menstruation remains normal, may interfere with libido. In some cases of endometriosis treated by continued steroid therapy with suppression of menstruation, libido is lost completely though perhaps transiently.[11]

At present the steroids are expensive and their large-scale use would require Governmental subsidy. Perhaps twenty years must elapse before we can judge whether the possible deleterious effects of suppressing ovulation by long-continued steroid therapy outweigh the benefits. Meanwhile, at a rate of rather more than 1 per second, world population may have increased by some 700 million.

Clubbing of the Fingers and Osteoarthropathy

DESPITE the antiquity of the original Hippocratic observations, the causes of finger clubbing remain obscure. The association of clubbing with lung disease or cyanotic heart-disease is well established. The condition has also been related to extrapulmonary disorders, but without satisfactory evidence that coexisting lung lesions have been excluded. In its early stages clubbing —that is to say, expansion of the ends of the digits—is difficult to recognise.[12] No such difficulty arises in hypertrophic pulmonary osteoarthropathy, where gross clubbing is associated with joint swelling and pain and with symmetrical periostitis in the shafts of long bones.[13 14] Hypertrophic osteoarthropathy generally accompanies peripheral bronchial neoplasm,[15 16] and less commonly other pulmonary lesions such as pleural tumours [17] and bronchiectasis.[18 19] Idiopathic [20] and hereditary [21] forms have also been reported.

There is a surprising dearth of data on the frequency of clubbing or osteoarthropathy in various diseases. Clubbing was found in only 28 of 481 patients with operable carcinoma of the bronchus.[22] In the same series the prevalence of osteoarthropathy was estimated at 5%; but other workers have reported lower figures.[23 24] The prevalence of clubbing and osteoarthropathy is low in pulmonary tuberculosis and proven cases of bronchiectasis.[18 22] Clinical observation suggests that clubbing is commoner in patients with arteriovenous aneurysms of the lung, subacute bacterial endocarditis, or cyanotic congenital heart lesions; but hypertrophic osteoarthropathy is extremely rare in congenital heart-disease.[25] CUDKOWICZ and WRAITH,[26] in a detailed study of 27 patients with different lung diseases and gross finger clubbing, detected no common clinical factor. MENDLOWITZ [19] suggested that arterialde saturation and increased blood-flow to the fingers with a decrease in the gradient of brachial arterial pressure played a part. Evidence of increased blood-flow to the distal segment of the clubbed digit was found in cases of uncomplicated clubbing [27 28] but not in 3 cases of osteoarthropathy.[28] Experimentally the pulmonary artery was anastomosed to the left auricle in 4 dogs, 1 of which subsequently developed changes suggestive of pulmonary osteoarthropathy.[29] The main effect of this procedure was an increase in cardiac output and a reduction in arterial oxygen saturation. In man, however, clubbing of the fingers and pulmonary arthropathy are commonly found with normal arterial oxygen saturation—for example, in cases of subacute bacterial endocarditis and of small peripheral pulmonary neoplasms. Moreover clinical conditions associated with increased cardiac output, such as thyrotoxicosis, severe anæmia, or Paget's disease, are not complicated by osteoarthropathy. GINSBURG [30] found that hand and foot flow were similar in patients with hypertrophic osteoarthropathy and in a control group; forearm and calf flow were raised in only a small proportion of patients with osteoarthropathy. GINSBURG concluded that the periosteal lesions were not the result of an increase in total peripheral flow.

Relief of pain and joint swelling has been found to follow section of the vagus at the hilum of the lung in patients with inoperable pulmonary neoplasms and hypertrophic pulmonary osteoarthropathy.[31–33] This observation was held to indicate that a neural reflex produced osteoarthropathy. Unfortunately there are no measurements to show that cutting the vagus leads to subsidence of the periostitis, although clinically symptoms may be relieved. In a single case of arthropathy, the volume of the terminal inch of the right thumb was measured after vagotomy; no change in mass was recorded, though subjective improvement was apparent.[26] It is noteworthy, however, that GINSBURG [30] showed that peripheral flow was reduced after thoracotomy. FRIED [34] suggested that pituitary activity is altered in osteoarthropathy, but SEMPLE and MCCLUSKIE [24] were unable to confirm this. Possibly other endocrine abnormalities are present in such cases. Gynæcomastia is not uncommon,[35] and urinary œstrogen excretion was raised in 3 patients with arthropathy, though only 1 of these had gynæcomastia.[27]

10. Crosson, J. W. *Fertil. Steril.* 1959, **10**, 361.
11. Snaith, L. Personal communication.
12. Pyke, D. *Lancet*, 1954, ii, 352.
13. von Bamberger, E. *Wien. klin. Wschr.* 1889, **2**, 226.
14. Marie, P. *Rev. Méd.* 1890, **10**, 1.
15. Craig, J. W. *Brit. med. J.* 1937, i, 750.
16. Rotjer, E., Aguilar, H. D., Lasceles, M. C. *Rev. Sanid. milit., B. Aires*, 1947, **45**, 1163.
17. Price-Thomas, C., Drew, C. E. *Thorax*, 1953, **8**, 180.
18. Locke, E. A. *Arch. intern. Med.* 1915, **15**, 659.
19. Mendlowitz, M. *Medicine, Baltimore*, 1942, **21**, 269.
20. Camp, J. D., Scanlan, R. L. *Radiology*, 1948, **50**, 581.
21. See *Lancet*, 1955, i, 340.
22. Wierman, W. H., Clagett, O. T., McDonald, J. R. *J. Amer. med. Ass.* 1954, **155**, 1459.
23. Jack, G. H. *Lancet*, 1952, i, 750.
24. Semple, T., McCluskie, R. A. *Brit. med. J.* 1955, i, 754.
25. Trever, R. W. *Ann. intern. Med.* 1958, **48**, 660.
26. Cudkowicz, L., Wraith, D. *Brit. J. Tuberc.* 1957, **51**, 14
27. Mendlowitz, M. *Clin. Sci.* 1938, **3**, 387.
28. Mendlowitz, M. *J. clin. Invest.* 1941, **20**, 113.
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30. Ginsburg, J. *Quart. J. Med.* 1958, **27**, 335.
31. Brea, M. M. *in* Year Book of General Surgery; p. 306. Chicago, 1948. *Lancet*, 1957, ii, 194.
32. Hansen, J. L. *Acta med. scand.* 1952, **142**, suppl. 266.
33. Flavell, G. *Lancet*, 1956, i, 260.
34. Fried, B. M. *Arch. intern. Med.* 1943, **72**, 565.
35. von Bamberger, E. *Z. klin. Med.* 1891, **18**, 193.

MENDLOWITZ [36] has suggested that the key to the phenomenon of clubbing lies in the pulmonary circulation. Whilst this concept does not account for unilateral or unidigital clubbing, there is evidence of a left-to-right shunt through the lung in patients with bilateral clubbing. By injection studies at necropsy, CUDKOWICZ and ARMSTRONG [37] detected precapillary anastomoses between the bronchial arteries and peripheral pulmonary arteries in cases of lung disease associated with finger clubbing. In patients with finger clubbing differential catheterisation of lobar branches of the pulmonary artery has shown that the oxygen content of blood samples taken from unwedged catheter positions in a branch close to a tumour or bronchiectatic lobe is more highly arterialised than blood obtained in similar positions from branches supplying normal lobes. [38] This suggests an increased bronchial arterial blood-flow, entering the pulmonary artery bed proximal to the capillaries in diseased parts of the lung. FISHMAN et al.,[39] using a modified Bloomer technique,[40] recorded abnormally high flows in the bronchial arteries of patients with idiopathic clubbing of the fingers. The significance of high bronchial arterial flow through precapillary bronchopulmonary anastomoses in patients with bilateral clubbing or osteoarthropathy is undecided. HALL [41] has lately suggested that clubbing is associated with reduced ferritin passing unchanged through pulmonary arteriovenous shunts; while DOYLE [42] believes that hypertrophic pulmonary osteoarthropathy is an œdema resulting from excessive stimulation of volume receptors in the pulmonary artery. The evidence for these hypotheses is by no means complete; but the discrepancy between them underlines the need to regard these two disorders as separate entities.

Varicose Veins

OPINION on the management of varicose veins is sharply divided. Some surgeons do not believe that much can usefully be done, so content themselves with a brief patching-up operation or pass the patient on to a junior colleague. To other surgeons varicose veins are a mechanical problem, pure though complex, that can be solved—given knowledge, skill, care and time. How much benefit surgery can really provide is unlikely to be known until some of the attention now concentrated on flow mechanics is diverted to the underlying pathology of the veins—and perhaps of all vessels. On the other hand, even if complete and permanent cure cannot yet be guaranteed, operation can result in great and long-lasting symptomatic relief.

DODD [43] has done a valuable service in once again drawing attention to the short (external) saphenous vein. Since 1953, stimulated by the work of COCKETT and JONES,[44] he has made a special study of the short saphenous system in all his varicose-vein patients; and he reports that in a seventh of all cases (a rather higher proportion than that mentioned by other investigators [45 46]) this vein was abnormal. Moreover, as more and more of these veins are explored, "two other features are emerging: first, because of the variability of its termination, there may be difficulty in exposing its ending, except with a large incision; and second, in some patients, after it has been divided flush at its union with the popliteal vein, and its trunk stripped out at the ankle, considerable varices remain". In a passage of wit and wisdom HENRY [47] has described the crucial region where the short saphenous vein—the "blue guide to the midline"—joins the popliteal vein; but the first knife-strokes in his bloodless approach are commonly a signal for torrential hæmorrhage. The fault lies not with HENRY; for the "normal" venous pattern of the limbs is but a point of departure to almost infinite variations. KOSINSKI [48] gave a good account of the most important of them in 1926; and, whereas "until recently these were seldom found, because they were seldom looked for . . . now that a full dissection of the popliteal space is being made, they are being increasingly recognised".[43] But such a full dissection demands time; and time it seldom gets. Usually the surgeon, having dealt with the long (internal) saphenous vein, has two alternatives. He can either turn the patient on his face, rescrub, and retowel; or, with the aid of sandbags, spotlights, and elastic bandages, he can insinuate a scalpel and an artery-forceps or two where textbooks say the short saphenous joins the popliteal vein.

Unfortunately the most effective surgical therapy is also the most difficult. The original high ligation of the long saphenous vein and its branches (whether or not supplemented by a course of injections) had an early recurrence-rate of over 50% [48–50]; but it was simple, safe, and capable of being standardised. The gradual realisation since the 1930s that varicosities often develop from sources other than an incompetent saphenofemoral junction (coinciding with the introduction of stripping, venography, and other technical advances) has inaugurated a more rational therapeutic era but has also created new problems.[51–53] Previously patients suspected of having deep-vein thrombosis were excluded from surgical treatment. But LINTON, DE TAKATS, and others began to ask whether patent but incompetent deep veins, far from conveying blood, did not aggravate venous stasis; LINTON [54 55] and his group went so far as to advocate ligation of the femoral vein in order to prevent reflux through incompetent perforators into superficial channels, and BAUER [56] applied the same principle at the popliteal level. Results were not altogether encourag-

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37. Cudkowicz, L., Armstrong, J. B. *Brit. J. Tuberc.* 1953, **47**, 227.
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41. Hall, G. H. *Lancet*, 1959, i, 750; *ibid.* p. 1151.
42. Doyle, L. *ibid.* pp. 989, 1253.
43. Dodd, E. *Brit. J. Surg.* 1959, **46**, 520.
44. Cockett, F. B., Jones, D. E. E. *Lancet*, 1953, i, 17.
45. Foote, R. R. Varicose Veins. London, 1949.
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47. Henry, A. K. Extensile Exposure applied to Limb Surgery. Edinburgh, 1945.
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53. Myers, T. T. *J. Amer. med. Ass.* 1957, **163**, 87.
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56. Bauer, G. *Angiology*, 1955, **6**, 169.

ing. Uncertainty still prevails about where, when, and what can be ligated with impunity [46 57–60]; but most surgeons have come to the conclusion that bad veins are better than no veins; and the accurate localisation and ligation of all incompetent perforators (what DE TAKATS [46] calls the "third era" in the surgical treatment of varicose veins) seems to offer a reasonable compromise. Reasonable, and successful, too; but technically not easy. To explore the gastrocnemial veins, the veins of the biceps and semimembranosus, the calf communicating veins, as well as the short saphenous vein [43] is no task for the beginner or even for the master in a hurry.

Under favourable conditions venous dissections are the ideal exercise for young surgeons; but conditions, far from being favourable, are usually appalling. To expect the harassed registrar to "polish off" a couple of "v.v.s" at the end of a long operation list is bad enough; but "v.v." sessions by house-surgeons in the casualty theatre are still not just a memory.

Annotations

BEDS FOR CONFINEMENT

IN London many women who are told to have their babies in hospital are also told that no bed can be booked for them in advance. With hospitals so hard-pressed, this arrangement is understandable; but it is also intolerable. Repeatedly the Emergency Bed Service has drawn attention to the plight of the woman in labour for whom a bed —somewhere—has to be found at the last moment; and on p. 398 Dr. Abercrombie shows again that this is happening more often—not less often as one would expect. Far from being just an occasional administrative accident, it seems to be accepted as something normal and inevitable.

Of course it is not inevitable at all; and there are at least three possible ways of avoiding it that need to be considered by obstetricians, midwives, and administrators —jointly determined on effective action. The first is to find more beds. Difficult though this may sound, it should not be dismissed out of hand. If the demand were really accepted as a matter of urgency, old houses in some areas could be rapidly transformed into maternity homes for "normal cases", staffed by midwives and general practitioners genuinely interested in obstetrics. Secondly, the conditions on which a woman qualifies for a hospital bed could be made stricter. This again is difficult, because obstetrically the list of indications for admission grows ever longer, and the circumstances of many homes make them unsuitable for confinements. Nevertheless some hospitals, feeling that only the best is good enough for their own patients, are inclined to admit women whose claims to hospital confinement are tenuous; and there may be room for a little economy here.

What would transform the whole situation, however, would be a change of attitude toward the use of hospitals for "lying in". After a normal, or even a moderately abnormal, labour there is no need for the mother to stay in hospital for ten or twelve days. Though the advantages of *confinement* in an institution are increasingly evident, there are often real advantages, both for the mother and her child, if she "lies in" at home.[1] Provided domestic help can be arranged, many mothers could and should be sent home by ambulance 24–28 hours after delivery, before their milk comes in. The objection always raised to this suggestion is that midwives do not like "second-hand" cases; and in this they are not unreasonable, though sometimes the objection may have to be overruled. But once the principle of immediate return home were accepted, it should not be impossible to organise a maternity service in which the midwives or general practitioners took their own patients to hospital, delivered them there with whatever assistance might be needed, and continued to attend them on their return home.

These suggestions can no longer be dismissed as impracticable. In various forms they have already been tried and have worked. The present system in London, on the other hand, is clearly not working in a way that we can continue to accept.

TEACHING PATHOLOGY

ANXIOUS to encourage the introduction of the preventive aspects of medicine at an early stage into the undergraduate curriculum, the World Health Organisation has set inquiries in motion into how this may be achieved. Last year a study group explored the possibilities in physiology, and now an expert committee has reported [2] on its deliberations into what can be done in this direction in the teaching of pathology.

The committee held that the presentation of pathology as an undergraduate subject should not be confined to any single year but should be spread over the greater part of the entire curriculum. By ample treatment of general and experimental pathology, the teacher could lay a proper foundation for the two fundamental studies of ætiology and pathogenesis, on a proper understanding of which the scientific application of preventive measures depended. Pathology should form part of a course which was closely integrated with microbiology, radiobiology, and immunology on the one hand, and with clinical medicine and surgery on the other. In the committee's view the teaching of the preventive aspects of pathology gained much if it was depicted against a historical background of concurrent social and medical advances. Such illustrations could not fail to impress the student with the possibilities inherent in a preventive approach.

Although modern pathology now had a very broad scientific basis, its morphological aspects still retained, the report declares, a central position. A comprehensive necropsy service made an invaluable contribution to the health of any community; and the postmortem examination was one of the most appropriate stages in the medical course for the inculcation of ideas of prevention in the minds of both clinicians and students. For these and other reasons, the development of an effective necropsy service should be encouraged in all countries as an adjunct to both medical teaching and practice.

The importance of collaboration between pathologists and epidemiologists was one of the committee's main points. In time, social changes in many countries, especially those now relatively undeveloped, would

57. Schneewind, J. H. *Ann. Surg.* 1954, **140**, 137.
58. Straffon, R. A., Buxton, R. W. *Surgery*, 1957, **41**, 471.
59. Sherman, R. S. *Ann. Surg.* 1944, **120**, 772.
60. Sherman, R. S. *ibid.* 1949, **130**, 218.

1. FitzGerald, T. B. *Lancet*, 1959, i, 403; see also 1959, i, 397.
2. Preventive Aspects in the Teaching of Pathology. Seventh Report of the Expert Committee on Professional and Technical Education of Medical and Auxiliary Personnel. *Wld Hlth Org. techn. Rep. Ser.* 1959, **175**. Pp. 30. 1*s.* 9*d.* Obtainable from H.M. Stationery Office, P.O. Box 569, London, S.E.1.

demand that increased attention be given to epidemiological records; and by aiding in the collection of reliable statistics the teacher of pathology could contribute effectively to this work. Moreover, much important statistical information on morbidity and mortality was to be gained in general practice, in which a large proportion of students would ultimately be engaged, and the teacher of pathology should train the undergraduate in accurate recording so that he could make the most of these opportunities.

HEPATIC JAUNDICE

THE differential diagnosis of jaundice is generally straightforward, and only rarely is the diagnosis still in doubt after the usual clinical and laboratory investigations.[1 2] The main diagnostic problem in most of these doubtful cases is whether the jaundice is due to extrahepatic obstruction or to so-called intrahepatic cholestasis, which is most probably a variant of viral hepatitis. The differentiation is important not only because the treatment of the two conditions is so different, but because laparotomy, which is essential in extrahepatic obstruction, is extremely dangerous in patients with intrahepatic obstruction. Unfortunately, even aspiration biopsy has failed to resolve the problem completely, since the histological features of the liver in these two types of jaundice have much in common.

In order to restudy this whole problem Shorter et al.[3] selected 59 out of a consecutive series of 229 liver biopsies on the ground of discrepancies between the clinical, biochemical, and histological findings. The patients, who were seen at St. Thomas's Hospital, London, between 1952 and 1957, were followed up at least until the correct diagnosis became apparent. The results are both disturbing and encouraging—disturbing because several clinical and laboratory findings generally regarded as diagnostically reliable are here shown not to be so, and encouraging because histological minutiæ have been revealed that may provide a far more reliable basis for differentiation.

Among the misleading clinical features two were outstanding: (1) the presence of upper abdominal pain in some cases of intrahepatic obstruction and its absence in many cases of gallstone obstruction; and (2) the presence of splenic enlargement in several cases of extrahepatic obstruction. Of the biochemical findings usually regarded as of diagnostic help, the serum-alkaline-phosphatase level was shown to be quite unreliable as were also the various flocculation reactions; but a normal serum-albumin level was found to correlate fairly well with an extrahepatic lesion.

Of the various histological features to which particular attention was paid, necrosis of the parenchymal cells of the liver was common in both types of case, but the degree and type of inflammatory response was strikingly different. In extrahepatic obstruction the inflammatory response to the necrotic liver cells was relatively slight, commonly consisting of polymorphs, while in the intrahepatic cases the cell reaction was usually severe and predominantly mononuclear. Other findings mainly associated with extrahepatic obstruction were œdema and early fibrosis of the portal tracts, and proliferation of apparently normal bile ductules. Intrahepatic obstruction on the other hand was more commonly associated with an atypical type of ductule proliferation, pronounced variations in liver-cell nuclei, formation of giant liver cells, and formation of pseudoductules from regenerating liver cells.

On the basis of these and other features Shorter et al. suggest that aspiration biopsy of the liver is the safest and most reliable method of differentiating the two common types of hepatic jaundice when other methods have left the diagnosis in doubt. This conclusion has been derived from a retrospective study in which the criteria for differentiation were established by correlating the histological and the clinical data. Confirmation by a prospective study would mark a major advance.

1. Movitt, E. R. *Ann. intern. Med.* 1954, **40**, 932, 952.
2. *Lancet*, 1954, ii, 695.
3. Shorter, R. G., Paton, A., Pinniger, J. L. *Quart. J. Med.* 1959, **28**, 43.

NODULAR GOITRE AND THYROID CANCER

SINCE the late war many articles have appeared in the United States describing a high incidence of carcinoma in nodular goitres. One of the earliest and most influential papers was that by Cole et al.,[1] who found evidence of malignancy in 24% of uninodular and 11% of multinodular goitres. Most subsequent American reports have cited somewhat lower figures, and Sokal [2] estimates the overall prevalence of malignancy in excised nodular goitres at about 8%. In this country Branson and Houston [3] found that 12% of nodular goitres were histologically malignant. These workers concluded (like many of their American counterparts) that all nodular goitres should be submitted to thyroidectomy.

In general these reports were received here more sceptically than in the United States. They seemed to conflict with everyday experience, for clinicians know that nodular goitre is very common, but thyroid cancer very rare. The well-known difficulties in the histological diagnosis of this form of cancer seemed a possible explanation, although not applicable to the series of Cole et al.,[1] since 11 of 16 cancer patients were dead within five years of thyroidectomy.

Another possibility is that the reported series of nodular goitres, coming as they mostly do from well-known thyroid clinics, are highly selected and do not represent the general run of nodular goitres. This view has been ably expounded by Sokal.[2] He estimates that the prevalence of nodular goitre in the United States is of the order of 30,000 to 40,000 per 1,000,000 population, compared with about 25 thyroid cancers per 1,000,000 population. Hence among the total population of persons with nodular goitres the prevalence of thyroid cancer is less than 0·1%, compared with about 8% among persons with nodular goitre submitted to thyroidectomy in well-known clinics. This suggests that extremely powerful selection is at work, thyroid clinics receiving the greater part of those nodular goitres which are likely to be malignant. What is interesting about this process is that it appears at first sight to be unintended. Nearly all thyroid surgeons agree that they can seldom distinguish clinically between a benign and a malignant nodular goitre. The process may, however, be unintended only so far as the thyroid surgeon is concerned, for he is largely unaware of the selection which goes on before the patient reaches his clinic. This selection is no doubt made partly by physicians and general practitioners; but probably much is done by the patient himself. We do not perhaps always concede that what we are apt to refer to as our " clinical material " has quite a lot of common sense. A middle-aged woman

1. Cole, W. H., Slaughter, D. P., Rossiter, L. J. *J. Amer. med. Ass.* 1945, **127**, 883.
2. Sokal, J. E. *ibid.* 1959, **170**, 405.
3. Branson, K. M., Houston, W. *Lancet*, 1949, ii, 979.

would probably not worry her doctor about a lump in the neck which has remained unchanged for twenty years, but she would go to him if it started to get bigger. She is in a much better position to detect small changes in the volume of a goitre than any thyroid surgeon, even if he sees her more than once. The patients who finally appear in thyroid clinics therefore consist largely of those who find that their goitres are enlarging. It is not surprising that this group should contain most of the thyroid cancers.

If Sokal's interpretation is correct it would seem that the dispute about the incidence of malignancy in nodular goitre may be resolved. The thyroid surgeon is right in removing most of the nodular goitres which are presented to him: the patient is equally right in not getting alarmed about a nodular goitre which is not enlarging at all.

CATION-EXCHANGE RESINS IN ACUTE RENAL FAILURE

SYNTHETIC ion-exchange resins capable of removing anions or cations from solutions were first available in 1935, but were not used clinically until 1945,[1] when anion-exchange resins were given by mouth in an attempt to reduce gastric acidity in peptic ulcer patients. Later experience has proved this to be an ineffective treatment. Shortly afterwards Dock [2] showed that cation-exchange resins could remove sodium from the gastrointestinal contents and were useful in the treatment of œdema. Fourteen years later, cation-exchange resins are well established in the control of the œdema of congestive heart-failure and of the nephrotic syndrome, but often provoke hepatic coma [3] when given in cirrhosis of the liver.

The avidity of cation-exchange resins for cations of biological importance increases with rising atomic weight and valency:

$$Ca^{++} > Mg^{++} > K^{+} > Na^{+} > NH_4^{+} > H^{+}$$

When resins were first used in the control of œdema, they were given in combination with either hydrogen ion or ammonium. This caused undesirable potassium depletion as well as removal of sodium. This complication is now avoided by using resins in mixed ammonium and potassium form, which, however, somewhat reduces their capacity for sodium exchange. Elkinton et al.[4] first employed cation-exchange resins for removal of potassium in acute oliguric renal failure, thus avoiding death from the effects of hyperkalæmia on the heart. They used resins in the ammonium form, and gave about 50 g. daily either by mouth or by retention enema. Since then several additional papers [5–11] have confirmed the value of resins in this type of case. Whereas most American workers have preferred to use resins in the ammonium phase, resins combined with sodium have been more used in this country. Evans et al.[5] described their experience with a sulphonic cation-exchange resin combined with sodium ('Resonium-A'). They claimed that combination with sodium was preferable to ammonium because the resin did not intensify the acidosis resulting from the renal failure and did not increase the blood-urea. Administration of resin by retention enema was found to be much less efficient than by mouth. Evans et al.,[5] however, failed to note that a resin charged with sodium was less effective than an ammonium resin in removal of potassium, and that their results with resin given by enema were inferior to those of Elkinton et al.[4]

Palmer et al.[12] have recorded their more recent experience using a mixed hydrogen ion and sodium-charged resin given both by mouth and by retention enema. They recommend a mixture of $H^{+} : Na^{+} = 7 : 3$ to be given by intragastric tube, and $H^{+} : Na^{+} = 1 : 1$ by high retention enema. Usually resins charged with hydrogen ion cause ulceration of the mouth and œsophagus when taken by mouth. This was avoided by administration of the resin by intragastric tube, the stomach being well accustomed to high concentration of hydrogen ion. Presumably the lower concentration of resin charged with hydrogen ion recommended by enema indicates the lower tolerance of the colon to acid solution. The resins should be stored separately and mixed before use. This gives greater flexibility, since a lower concentration of hydrogen ion resin can be used if there is severe uræmic acidosis.

Their results are sufficiently impressive to warrant a change in the usual method used in this country of prescribing a resin completely charged with sodium, this being ineffective by enema. Resins frequently cannot be given by mouth owing to severe uræmic nausea and vomiting. The production of acidosis from resin is potentially less important now than in 1953 since several units are operating efficient artificial kidneys which can readily correct uræmic acidosis. Admittedly, hyperkalæmia is equally amenable to hæmodialysis, but resin treatment is still extremely useful in the treatment of cases where hyperkalæmia is disproportionate to nitrogen retention or uræmic acidosis. In addition, the uræmic patient can be transferred to an artificial kidney unit with much greater safety if the serum-potassium is within normal limits.

Significant hyperkalæmia is a problem in only a minority of cases of acute oliguric renal failure where there is little tissue damage or infection. Swann and Merrill,[13] reporting a large series of cases, gave an incidence of only 25%. Hyperkalæmia is, however, a serious matter in any case involving damage to voluntary muscle or other body tissues. Meroney and Herndon [14] reported that resin therapy was relatively ineffective in controlling the serum-potassium in acute renal failure in battle casualties in the Korean campaign. Loughridge et al.[15] described a case secondary to muscle necrosis from carbon-monoxide poisoning. Here the patient died just before treatment with the artificial kidney could be started. In such circumstances, biochemical and electrocardiographic control at least twice daily is essential, because there is often an abrupt and unexpected rise of plasma-potassium. In cases of this type, administration of resins can only play a small part, but it is still essential to use the best available method. A finely-ground resin charged with hydrogen ion is not commercially available in this country as a pharmaceutical product. The results of Palmer et al.[12] are sufficiently impressive to recommend that such a resin should rapidly

1. Segal, H. L., Hodge, H. C., Warson, J. S., Jr., Scott, W. J. M. *Gastroenterology*, 1945, **4**, 484.
2. Dock, W. *Trans. Ass. Amer. Phycns*, 1946, **59**, 282.
3. Gabuzda, G. J., Jr., Phillips, G. B., Davidson, C. S. *New Engl. J. Med.* 1952, **246**, 124.
4. Elkinton, J. R., Clark, J. K., Squires, R. D., Bluemle, L. W., Jr., Crosley, A. P. *Amer. J. med. Sci.* 1950, **220**, 547.
5. Evans, B. M., Jones, N. C. H., Milne, M. D., Yellowless, H. *Lancet*, 1953, ii, 791.
6. Knowles, H. C., Jr., Kaplan, S. A. *Arch. intern. Med.* 1953, **92**, 189.
7. Stock, R. J. *Bull. N.Y. Acad. Med.* 1952, **28**, 507.
8. Harthon, J. G. L., Sigroth, K. I. E. *Acta med. scand.* 1952, **144**, 230.
9. Strauss, M. B., Raisz, L. G. *Arch. intern. Med.* 1955, **95**, 846.
10. Gailitis, R. J., Lambers, G. H. R. *Illinois med. J.* 1956, **110**, 214.
11. Danowski, T. S., Mateer, F. M. *J. chron. Dis.* 1957, **5**, 122.
12. Palmer, R. A., Price, J. D. E., Eden, J. *Canad. med. Ass. J.* 1959, **80**, 432.
13. Swann, R. C., Merrill, J. P. *Medicine, Baltimore*, 1953, **32**, 215.
14. Meroney, W. H., Herndon, R. F., Jr. *J. Amer. med. Ass.* 1954, **155**, 877.
15. Loughridge, L. W., Leader, L. P., Bowen, D. A. L. *Lancet*, 1958, ii, 349.

be made available. Resins charged with sodium have already saved many lives, but there is little doubt from the available evidence that resins charged with hydrogen ion would be much more potent in hyperkalæmia where treatment by enema is indicated.

A WORLD SCENE

IT usually does good to any organisation if from time to time someone in authority sits down to ponder upon its aims, methods, and achievements, and then commits his thoughts to paper. Slowly and sometimes unnoticeably problems change and their solutions too, and day-to-day routine may distort the best of plans. An occasional review gives the opportunity for a new start. This is what the World Health Organisation has just done, and the report of its director-general, Dr. M. G. Candau deserves notice.[1]

About a quarter is occupied by a thoughtful survey of the way in which the Governments of the world care for the health of their peoples; their methods of medical education and of recording illness; the major problems of public health; and the work which remains to be done—and there is quite a lot of this. Nothing could be more admirable than the synthetic and scholarly approach to this task, and anyone who is deeply stirred by jingo loyalty to "his own" system will read this with advantage. Some countries have abolished the profit motive in medicine while some rely upon it very largely, but no-one would be able to discover the prevalent economic theory from the mortality statistics alone. Such objective data give just as little help in finding "the best" system of medical education. In countries whose traditions of teaching stem from Germany, the theoretical basis of medicine derives from morbid anatomy; in others the study of symptoms seems to be the foundation of clinical practice. In both, infant mortality tends to fall and the expectation of life increases every year. Public-health measures are likely to fail in only two kinds of country—where the will or the money is lacking, or where the inhabitants are so sure of the rightness of their methods that no others are tried. All the others will progress, quickly or slowly, by learning from others and at the same time modifying methods to suit local conditions. Nothing illustrates this better than the history of anti-malarial measures. Once the life-cycle of the plasmodium was known it was clear that it might be interrupted at several points; but slowly and bitterly the experts learned that the measures which might be effective in Ceylon failed in Malaya and Holland.

The rest of the book consists of an account of the health of individual countries, each considered as an independent area but grouped in geographical regions. To each is given a topographical introduction and a rather diffuse account of the organisation of the health services and the major problems which they face. There is no reason to doubt the accuracy of any of this, but its usefulness is limited. To begin with, space has been allocated somewhat arbitrarily. India (pop. 380 million) has four columns, Denmark (pop. $4^1/_4$ million) rather more than eight; and the medical problems of the first are quite considerable. The information comes from official sources, and few countries like to admit that some of their inhabitants do not get enough to eat; so malnutrition is seldom mentioned. For much the same reason the book is not a reliable source of information on, for instance, the survival of malaria in Europe: that the disease is not mentioned does not mean that it is extinct. Figures for morbidity and mortality are rare. Sometimes, we know, they do not exist. The introduction remarks that such facts require evaluation: they do, but some doubting Thomases will want to make their own evaluations. It gives little confidence to read that "steps have been taken" to protect several million inhabitants against trypanosomiasis: for fifty years quite considerable steps have been taken to protect us against sudden death on the road. If these national surveys had been cast as answers to a questionary they would have taken half the space and made it easier for the reader to discover the answer to specific questions.

"World" and "global" are words which have gained unspoken extra meanings since 1945 ("patriot" and "progressive" acquired similar moral increments at earlier stages in our history). W.H.O. works hard to live up to their implications, and its absence of national bias would probably have seemed impossible before 1918—or even later. There are times, however, when a little plainer speaking would perhaps be profitable. The secretariat knows that vital statistics from Holland are more reliable than those from British Guiana or Laos, but for many obvious reasons does not draw attention to the fact. There is no mention of the pilot surveys and demonstrations which have foundered in the intricacies of local politics. An innocent who read this book might wrongly deduce that progress is universal and uniform.

1. First Report on the World Health Situation. Official Records of the World Health Organisation, no. 94. Geneva: W.H.O. Obtainable from H.M. Stationery Office. P.O. Box 569. London. S.E.1. Pp. 392. 17*s*. 6*d*.

NATURAL RADIOACTIVITY

THERE is little new information (as opposed to speculation) on the dangers of radiation fallout from bomb testing; but in a paper last week to the British Association [1] Prof. W. V. Mayneord, Dr. R. C. Turner, and Dr. J. M. Radley gave some important new data on natural radioactivity. Their study, a continuation of work already reported,[2 3] was concerned with the occurrence and metabolism of natural α-ray emitters. These have provided a valuable guide to the hazards of living in a naturally radioactive world, and hence also in one contaminated by man-made fission products.

Mayneord and his colleagues have shown, among other things, that, while there is a tenfold variation in concentration of natural radioactivity between different individuals in the United Kingdom, about a quarter of this activity is contained in soft tissues and particularly the thyroid and lungs. They have shown, too, that radioactive bone content does not apparently increase with age. In a metabolic experiment on a $3^1/_2$-year-old boy they found that 80% of ingested natural radioactivity in food was excreted within 48 hours. These workers have also investigated the distribution of natural α-ray emitters in foodstuffs and found that the content varied from low levels in fruit and vegetables to medium levels in materials such as meat, fish, milk, and cereals (in that order) and a relatively high level in brazil nuts: four ounces of brazil nuts contains as much radioactivity as the "average" human body.

Information of this type, by providing a baseline of body radiation dose resulting from natural radioactivity, may help us to assess more accurately the relative and

1. *Times*, *Guardian*, and *Daily Telegraph*, Sept. 9, 1959.
2. Turner, R. C., Radley, J. M., Mayneord, W. V. *Nature, Lond.* 1958, **181**, 518.
3. Turner, R. C., Radley, J. M., Mayneord, W. V. *Health Physics*, 1958, **1**, 268.

actual hazards of man-made radioactivity—including fallout. The work of Mayneord's group suggests that there may be a biological mechanism (in man, at least) for keeping down the body content of radium and thorium—i.e., some biological mechanism capable of maintaining radioactive balance at least under normal conditions. This suggestion has been made before, though with fewer facts to support it. In the radioactive areas of Kerala, where thorium-containing monozite sands account for natural backgrounds of up to ten times those elsewhere in the world, a survey of the exposed population is projected, and in the light of preliminary observations Gopal-Ayengar [4] has remarked that at least superficially these people show no evidence of paying a genetic or somatic price for the residence of themselves or their ancestors in Kerala—though possibly, as he says, the price was paid many generations ago.

The new data underline the inadequacy of our knowledge of the metabolism of radioactive materials—knowledge on which our assessment of hazard (and hence of maximum permissible dose) depends. The fact that we have in the past underestimated the radiation content of food and underestimated the human metabolic machine is extremely important; and these findings will doubtless be the starting-point for further work. Meanwhile there is, so far as we are aware, no evidence at all that should lead us to discount the danger from radioactive fallout.

STAPHYLOCOCCAL PNEUMONIA

THE notoriety which staphylococcal pneumonia has lately achieved gives the impression that its incidence is increasing, perhaps as a result of the widespread use of antibiotics. Ede et al.,[5] however, find no grounds for alarm: whereas their study of the available evidence suggested that in the pre-antibiotic era the staphylococcus was responsible for 9% of acute pulmonary infections, these workers found that it was the ætiological agent in only 25 (1·5%) of 1654 cases of acute pneumonia admitted to their hospital from 1956 to 1958. The mortality-rate in their series was also comparatively low: out of a total of 36 patients with staphylococcal pneumonia treated since 1956 only 1 died. They attribute their favourable therapeutic results partly to the fact that in most cases the infection was acquired outside hospital; for in 4 in which it seemed likely that drug-resistant "hospital organisms" were the responsible pathogens the disease was severe, advanced rapidly, and was difficult to control.

Because of the special dangers associated with staphylococcal pneumonia early diagnosis is important so that appropriate treatment can be given without delay, and Ede et al. draw attention to possible clues which should alert the clinician: dyspnœa out of proportion to the clinical findings; a dusky cyanosis of lips and nail-beds; little chest X-ray change in the first 24–48 hours; pleural pain; empyema or bronchopleural fistula; the formation of bullæ; and involvement of several lobes or of an entire hemithorax. Sensitivity tests will indicate the appropriate antibiotic; but while the results are awaited it is unwise, as Ede et al. point out, to rely on penicillin or tetracycline if the patient is severely ill and staphylococcal pneumonia seems a possibility; in these circumstances a combination of chloramphenicol and erythromycin, or of novobiocin and erythromycin, is safer. Empyema with or without bronchopleural fistula is notoriously common in staphylococcal pneumonia, and is apt to result in gross pleural thickening with associated loss of lung function. A complaint of pleural pain should prompt a search for fluid, and Ede et al. suggest that if it is discovered the immediate institution of closed-tube drainage with a large catheter may obviate the necessity for lung decortication later.

LENS REGENERATION

IN mammals, regeneration of specialised tissue is exceptional and slight; but ophthalmologists are aware from daily observation that—rather surprisingly—some regeneration of lens fibres is not uncommon. Such regeneration raises a problem in extracapsular extraction of cataract; for the capsule left behind tends to get denser with time, and this denseness is not exclusively due to opacification of the capsule, but results from some new lens fibres. While oculists were very much concerned with this problem as long as some century and a half ago, experimental embryologists have become interested only quite recently. The determining role of the optic cup came to be appreciated from rather startling findings—for instance, that in the chick embryo the optic cup would build a lens out of any ectodermal tissue with which it was in contact: a lens could be made out of ectoderm that was destined to become abdominal skin if the optic vesicle was transplanted on to the abdomen. Later, regeneration of a missing lens became a tantalising problem with the successful work on the amphibian eye by Stone and others. Now Russian workers have shown that regeneration of a high order is possible in the mammalian eye—so much so that one of these workers, P. S. Chanturishvili,[1] could speak hopefully last year at the Oxford Ophthalmological Congress of clinical possibilities.[1] Apparently these lens fibres are derived from cells which are neural in origin, and which require for the initiation of fibre formation the products of cytolysis of epidermal elements.

Chanturishvili and his associates have shown that when small fragments of cytolysing fœtal tissues are introduced into the lens capsule of adult rabbits, from which all easily separable contents have been evacuated, regeneration will take place, giving something like a normal lens in contrast to the incomplete formation of lens fibres that are seen in untreated aphakic eyes. The detailed experimental results reported at Oxford last year are now confirmed in a preliminary study by Stenhouse Stewart and 'Espinasse [2] of Hull. So far, experimental studies suggest that the regeneration of lens follows more readily on the evacuation of healthy lens matter from a mammalian eye than on the removal of cataractous lenses. Satisfactory regeneration of lenses in rabbits have, however, been obtained by Sikharulidze [3] after removal of chemically induced cataracts. Studies on these lines are now proceeding at Hull, where cataract is being produced by local irradiation.

In his experiments, Chanturishvili used conserved minced brain of mice as the necessary neural agent to initiate fibre production in the capsule of the extracted lens of rabbits. What other material can be used for this purpose is apparently still not decided. Despite the considerable theoretical and practical difficulties raised by this work, a substantial advance with clinical possibilities has clearly been made.

4. Gopal-Ayengar, A. R. (in the press). Paper presented to the radiobiology section of the International Congress of Radiology, Munich, July, 1959.
5. Ede, S., Davis, G. M., Holmes, F. H. *J. Amer. med. Ass.* 1959, **170**, 638.

1. *Trans. Ophthal. Soc. U.K.* 1958, **78**, 411.
2. Stewart, D. S., 'Espinasse, P. G. *Nature, Lond.* 1959, **184**, 1815.
3. Sikharulidze, T. A. *Bull. Acad. Sci. Georg. S.S.R.* 1956, **14**, 337.

Special Articles

AN ALCOHOLIC UNIT IN A MENTAL HOSPITAL *

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THE work of the small treatment centre for alcoholics in a mental hospital which was described in these columns four years ago (Glatt 1955a) has now gone on for seven years, and a further report may be of interest.

THE PATIENTS

Over 250 alcoholics entered Warlingham Park Hospital between 1952 and 1956 as voluntary patients, of whom two-thirds were men.

A third of all the patients were under forty years of age; most of them fell into the age-group forty-one to fifty years; the average age among women was three and a half years higher than among men. Only a fifth were married and still living with their spouses. Of the married women two-thirds had lost their husbands by death, divorce, or separation—a statistically significantly higher proportion than among the married men.

Most men were of high-average to superior intelligence, most women of average intelligence. Half the men belonged to social (occupational) classes I and II. Clinical observation and Rorschach tests indicated many different types of personality. A Rosenzweig Picture Frustration Test showed many extrapunitive and few impunitive reactions (Bathurst and Glatt 1959). On the basis of Henderson and Gillespie's description (1956), and from a review of their history and conduct in hospital, about two-thirds were classified as non-psychopathic and a third as psychopathic. Thiamine deficiency and impairment of liver function (usually reversible) were not infrequently demonstrated by laboratory tests (Kay et al. 1959) despite the absence of clinical abnormalities. A fifth of the patients had a history of suicidal attempts, and a similar proportion had taken drugs to excess.

Patients were referred to the unit from other hospitals, Alcoholics Anonymous (A.A.), observation wards, and probation officers, and in recent years more have been sent to us by general practitioners. The high proportion of the patients from higher social-class and intelligence groups was most obvious among the A.A. referrals (Glatt and Whiteley 1956).

CASE-HISTORIES

The patients' drinking careers were studied by a slightly modified form of Jellinek's questionnaire (1946) with 107 questions. From the replies the following picture of hypothetical average patients emerged:

The *male* patient had become a regular heavy drinker in his mid-twenties, had shown premonitory signs of alcoholism in his early thirties, and definite signs—e.g., loss of control over his drink intake—in his mid-thirties. Yet he was first admitted to hospital for alcoholism only at the age of forty. In a small minority definite signs of alcoholism appeared much earlier and led to hospital admission in their early twenties. On the other hand, a few did not start to drink to excess until in their late forties, often after a period of severe emotional stress.

The *female* patient had been a regular moderate drinker in her mid-twenties and occasionally got drunk in her early thirties. Premonitory signs of alcoholism—such as surreptitious drinking, drinking before parties, and amnesias—had appeared in her mid-thirties, and were soon followed by more obvious signs. The interval between first getting drunk and the first prodromal signs of alcoholism was only five years in the average female alcoholic compared with ten years in the male. Addiction thus seems to develop more rapidly in women than in men (Jellinek 1952).

The importance of such events as loss of control, morning drinks, solitary drinking, and repeated amnesias, in the development of alcoholism, is shown by their frequent occurrence in these histories and their relative rarity in the histories of a small control group of moderate drinkers who, at an average age of forty, had not shown signs of alcoholism.

RESULTS

By 1956, 94 patients had been out of hospital for two to three and a half years. About a third had had no relapse into drinking, another third was clearly improved (despite a few minor relapses), and the rest were either failures or untraced (Glatt 1959).

The results differed little from those of the earlier follow-up of the same patients six months to two years after discharge (Glatt 1955). Most first relapses occurred within six months of discharge from hospital, and they became less and less frequent afterwards. The results of a follow-up of a larger group of 182 alcoholic ex-patients six months to three and a half years after discharge were also the same (Glatt 1959). A comparison of results after longer and shorter observation periods showed that while a few " successes " had relapsed, others, who immediately after discharge had faltered, had kept in touch with the hospital aftercare services or with A.A., and had steadily improved.

Analysis of the follow-up of the 182 patients showed a statistically significant higher improvement-rate among men than among women, among the older than among the younger men, among the higher social classes than among the lower, and in particular among non-psychopaths than among psychopaths.

However there was a statistically significant difference between non-psychopaths and psychopaths in the relative proportions of male alcoholics who were older, highly skilled and intelligent, and married and still living with their spouse. To determine the true influence on prognosis of such factors as age and marital status, these subgroups were studied separately. Thus the fate of the unmarried psychopath was compared with that of the married psychopath, and so on. These results showed significant differences only in the improvement-rates of men as against women (among the non-psychopaths) and "probably significant" differences in favour of married men over the unmarried and separated (Glatt 1959).

Thus among our patients personality and, to a much lesser extent, sex seem to be the factors with the most definite bearing on prognosis.

DISCUSSION

Our programme, based on community living, group therapy (Glatt 1958a), close collaboration with A.A., drug therapy, and aftercare, has proved popular with the patients. The need for such a unit has been obvious from the number of requests for admission, most of which had to be refused for want of beds.

Most patients were of more than average intelligence and skill and belonged to potentially the most productive age-groups. Apart from humanitarian considerations, rehabilitation of these people would prevent great economic and financial loss, especially as their excessive

* Abridged from a paper which was successful in the 1958 research report competition of the South-West Metropolitan Regional Hospital Board.

drinking had been going on for many years before they were diagnosed and treated. The regular occurrence of premonitory signs fairly early in the alcoholic's drinking career is a challenge to offer earlier treatment. More widespread knowledge of the characteristic development of alcohol addiction (Jellinek 1952) would help in its prevention or early arrest, and all medical students should be taught to recognise these warning signs.

The present lay and medical view of the typical alcoholic is still uninformed, prejudiced, and unnecessarily pessimistic. The average alcoholic is neither asocial nor antisocial (Glatt 1958b). In most of our patients asocial or antisocial conduct started only after many years of heavy drinking, and was probably its result not its cause. Many other features ascribed to the alcoholic personality are probably due to ethical and possibly intellectual deterioration, and by the alcoholic's reactions to imagined or real social censure and pressure. The unselfish behaviour and the professional comeback achieved by many of our patients show that these personality changes are reversible.

Among our patients psychopathic features proved the most important prognostic factor.† Without a knowledge of the proportion of psychopaths in any series of patients it seems impossible to compare the results of different observers (Lincoln Williams 1952). Two-thirds of our patients showed over the years clear evidence of having benefited from their stay in hospital. Many former patients regularly revisited the hospital groups, attended the reunion meetings, established new A.A. groups, or took an active part in their local A.A. groups, and contributed to the monthly hospital magazine. Some of them organised meetings in their neighbourhood to which local doctors, clergy, magistrates, and others were invited, or helped to give talks to medical or lay audiences.

In hospital most of them were cooperative and their behaviour quite unlike the usual idea of the conduct of alcoholics. Admittedly our patients were not a true cross-section of the alcoholic population in this country, but they may be fairly representative of alcoholics who enter mental hospital (Glatt 1955b). Community living and group therapy should therefore be a feasible basis for treatment in other mental hospitals. There seems to be little justification for sending the alcoholic to the local mental hospital, where he is alone with his problem and where no special treatment is offered. Rightly or wrongly, he feels neither welcome nor understood: he complains, is labelled " uncooperative ", and leaves prematurely. His reaction is different when he finds himself in a therapeutic community formed by alcoholics, where he is treated by a team of experienced workers.

I firmly believe that regional alcoholic units, working in close collaboration with local A.A. groups, should replace the present unplanned and haphazard scattering of alcoholics to places where they feel they do not belong. The units could also become centres for research, education, and teaching.

I am indebted to Prof. E. M. Jellinek and the *Quarterly Journal of Studies on Alcohol* for permission to use their questionnaire; to Miss I. Lumb, F.P.S., and Miss P. A. Grigg, B.PHARM., for help with the statistics; to medical and other professional colleagues and many ex-patients for their cooperation and support; and in particular to the charge nurses of ward H1 at Warlingham Park Hospital, Mr. H. G. Thomas and the late Mr. F. S. Gray, for their understanding and untiring efforts.

References at foot of next column

† Some decrease in the number and severity of drinking bouts was apparent in a few psychopaths, but in the statistics they were included among the failures.

RECENT WORK OF THE EMERGENCY BED SERVICE

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KING EDWARD'S HOSPITAL FUND FOR LONDON

THE Emergency Bed Service (E.B.S.) has just celebrated its coming of age. In 1938, general practitioners received a neat card to say that, if they would ring a certain number and give details, a new department of King Edward's Hospital Fund for London would help them to secure prompt admission of their urgent cases to appropriate hospitals. Today, in Greater London, emergency admissions to hospital during the winter months amount on the average to a little over half the total of admissions, and about a fifth of the emergency admissions are made through the E.B.S., which deals with about 65,000 applications each year. Originally designed simply to save the time of the busy general practitioner, it has now become an index—in the opinion of experts at the Ministry of Health the most sensitive index they have—of the rise and fall of sickness among the people of London.

MATERNITY

Of the unusual features in the work of the past three years, perhaps the most unwelcome has been a startling increase in the volume of requests for urgent obstetric admission.

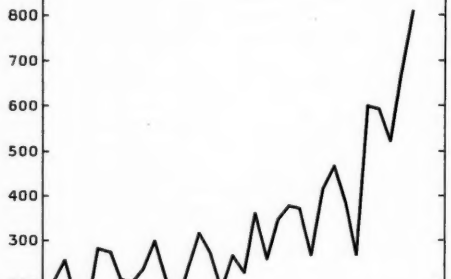

Fig. 1—Quarterly applications for urgent admission to maternity beds.

Fig. 1 shows, quarter by quarter, the number of such requests from March, 1951, to March, 1959. Up to 1955, these ranged from 150 to 300 or so, and were mainly on behalf of patients whose confinement had been planned at home, but in whom some unexpected complication had arisen during or immediately after labour, which was often premature. There were also patients who had never attended either a general practitioner or an ante-

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natal clinic, and for whom, therefore, no accommodation had been arranged. The recent increase, which has now raised the total to more than 800 in a three-month period, is due to the failure or inability of antenatal clinics to book a bed in hospital for patients whose homes are so unsuitable that confinement in hospital is necessary; although obstetrically, as far as can be foreseen, there is no abnormality. The result is that nothing is done until the patient goes into labour, when she is expected to get in touch with a doctor or midwife who, after visiting her to confirm the facts, will ask the E.B.S. to find a bed for her.

I need not point out how unsatisfactory such a method is for all concerned, for it is the very opposite of good antenatal care. It is galling for the doctor or the midwife, and it is unfair to the patient who must suffer unnecessary anxiety and inconvenience. Not seldom the baby has been born in unsuitable conditions at home or in lodgings before there has been time to find a bed, or in the ambulance on the way to hospital.

This last-minute stopgap device has been further bedevilled by a pernicious notion that the E.B.S. actually has empty beds at its command which it may allot to such emergencies. In this there is no truth whatever. The E.B.S. will always do its best to *find* a bed but it has *no* beds under its control.

It is not for the service to suggest remedies for the present state of affairs, but it is increasingly evident that the mounting obstetric demand calls for immediate action.

WARNING SYSTEM

During the summer of 1956 the warning system [1] was revised. Past experience seemed to show that serious difficulty over the admission of general acute cases does not arise until weekly applications exceed 1500, and the proportion of admissions through a medical referee [2] reaches 1 in 8. We therefore decided to abolish the "white" warning, which had never called for any specific action; to issue a "yellow" warning when applications reach 1500 a week *and* the proportion of cases admitted through referees exceeds 12·5% of all admissions; and to issue a "red" warning if the yellow proves ineffective, or the situation continues to deteriorate. These warnings are cancelled as the situation allows.

RECENT WINTERS

The past three winter seasons provide a remarkable series (fig. 2).

The winter of 1956–57 was phenomenally mild, resembling 1949–50 and 1951–52, and the new system never had to come into operation.

But the winter of 1957–58 began with a unique feature—a wave of influenza in October—which raised the moving weekly total to more than 1600. In that month 6408 applications were received, when 4000 would have been average. The epidemic waned rapidly, and applications, rather unexpectedly, were down to a normal level in November. However, another surprise was at hand, for the seasonal peak of activity began in December, a month earlier than usual, and continued throughout January. No fewer than 1989 applications were received in the week ending Jan. 2, the highest figure ever reached except in 1952–53. In the middle of January there was an unusual demand for the admission of infants with acute respiratory disease, and requests for cots increased steadily until mid-February. In the worst week 256 cases were dealt with in the 0–4 age-group, comprising 45% of all requests for admission for respiratory disease. The normal figure would be about 15%. No adequate explanation has been put forward.

A yellow warning was put out on Dec. 5, and was changed to red on Jan. 2. It reverted to yellow on Jan. 13, and was cancelled on Jan. 23, but had to be reimposed from Jan. 30 to Feb. 4.

In 1958–59, conditions were quiet and uneventful until mid-January, when the 1500 line was crossed. February presented an astonishing contrast to the two preceding years. Apart from 645 infectious-fever cases, an epidemic of influenza, together with spells of fog and of cold weather, almost precipitated a breakdown, for 8165 cases were offered, of which only 7531 (89·25%) were admitted. Anything below 90%, with a red warning in force, is a very serious situation. Weekly applications reached a peak at 2419 on Feb. 23, almost level with the week of the "great fog" in December, 1952 (2536 applications). This pressure, together with a high incidence of sickness among the nursing staff in hospitals, made it necessary to ask general practitioners to keep their less seriously ill patients at home if possible.

Warnings were in force as follows: Jan. 19–Feb. 2, yellow; Feb. 3–March 2, red; and March 3–10, yellow.

February, 1959, during much of which the service was finding 2000 beds a week, was a severe test of the warning system. It is instructive to recall that, when the system was evolved in 1951, it was thought that hospitals would reach saturation-point at 1100 cases a week, and that any demand in excess of this would fail. The response of the hospitals to a demand nearly twice as great was magnificent, and the service is most appreciative of their help and cooperation during this critical period.

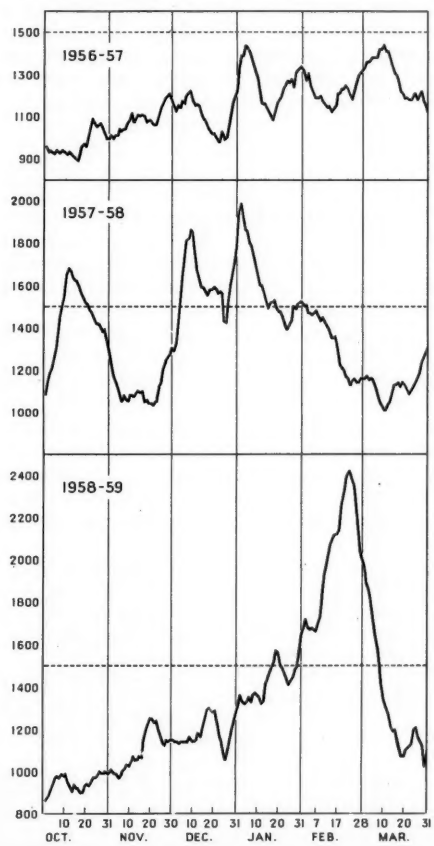

Fig. 2—Weekly totals of applications for admission as general acute cases.

1. Abercrombie, G. F. *Lancet*, 1953, i, 234.
2. Abercrombie, G. F. *ibid.* 1956, ii, 1039.

FORECAST

To judge whether the moving weekly total of general acute cases will continue to rise, or whether it will fall, gradually or suddenly, is notoriously difficult. It seems that severe pressure early in the season—say in October or November—is less serious than similar pressure later on in January or February, when hospitals are already overcrowded. However, there are some hard facts. The following table shows the number of applications, all admissions, and admissions through the medical referee for the first quarters of the past eight years:

Year	*No. of applications*	*No. of admissions*	*No. (and %) admitted via medical referees*
1952	14,891	12,834	705 (*5·4%*)
1953	21,197	17,642	2044 (*11·5%*)
1954	17,309	15,389	1955 (*12·7%*)
1955	18,106	16,250	2002 (*12·3%*)
1956	19,005	16,993	2633 (*15·4%*)
1957	15,982	14,914	1527 (*10·2%*)
1958	17,097	15,792	1888 (*11·9%*)
1959	20,125	18,746	2189 (*11·6%*)

That the percentage in the last column, so high in 1956, has declined appreciably is perhaps encouraging. The decline is to be attributed to the full use of the red warning in times of stress. But the less the referee procedure has to be used the better, for it is wasteful of time, money, and good will.

Next winter, if January, February, and March are mild, there may be only 14,000 or 15,000 casualties to be dealt with by the E.B.S.; but if the allies Cold and Fog are reinforced by Influenza, the number of casualties may well reach 21,000. Most will be the victims of respiratory disease,[3] and it would be well if hospital authorities made their plans sufficiently flexible to be able to accept very large numbers of such cases.

I am greatly indebted to the staff of the E.B.S., and particularly to Mrs. B. Williams, for help in the preparation of this paper.

3. Abercrombie, G. F. *ibid.* 1951, ii, 1175.

Points of View

THE ÆTIOLOGY OF LEUKÆMIAS
ILLUSTRATING AN ALTERNATIVE CONCEPT OF THE ÆTIOLOGY OF MALIGNANCY IN GENERAL

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WITH few exceptions (Lettré 1941, 1942a and b, Osgood 1957) scientists tacitly accept the idea that the reproduction-rate of cells depends on a balance between stimulating and inhibiting influences. This idea underlies nearly all work on malignancy, and it has led to the deadlock in which we find ourselves today.

An alternative hypothesis, which is based on the behaviour of unicellular organisms and of cells in tissue culture, is that cells have a natural tendency to continuous multiplication, which in multicellular organisms has to be restrained. Increases in the rate of reproduction result from decreased inhibition rather than from active stimulation. The degree of inhibition varies with the need for multiplication of the cells.

If this second hypothesis is correct, we may suppose that the cell's sensitivity to inhibition is localised to a well-defined part of the nucleus—in genes or complexes of genes. Inhibition will fail (and mitotic activity will be resumed) when the subtle interplay between cells and inhibitors is interrupted, either by a lesion of the " receiving genes " or by a deficiency of inhibitors. The result of a lesion of genes will be autonomous growth, while the result of defective inhibition will be a conditioned neoplasm.

Primary, local, autonomous growth arises when chemical, physical, or living agents penetrate the nucleus of one or more cells and damage the receiving genes of those cells (as part of a more extensive injury). If the damage is incomplete the cell will retain part of its sensitivity to inhibitors. The greater the damage, the less will be the sensitivity to inhibitory influences, and the more serious the malignancy. On this basis the well-known biological, chemical, and physical characteristics of cancer cells are to be interpreted as consequences, not causes, of the complex internal alterations in the injured nuclei. The causal agent, whether chemical, physical, or biological, must be small in comparison with the receiving genes—e.g., certain molecules, X rays, and viruses.

In *conditioned neoplasms*, inhibitors are not necessarily absent, but their quantity is subnormal. These tumours do not start in one cell, or a few, but may originate simultaneously in many cells which would normally be controlled by the missing inhibitor. At first these cells, though now dividing in quick succession, will not have neoplastic properties and their receiving gene complexes will remain intact. But long-continued serious deficiency of an inhibitor will produce secondary alterations in the corresponding receiving genes of conditioned tumour cells (Schöyer 1955).

For example, granulosa-cell tumours induced in mice by radiation are conditioned tumours, as appears from their readiness to react to normal quantities of inhibitor. In mice this inhibitor is present in both females and males, but it is neutralised in the latter by a testicular hormone. After re-implantation into females or into castrated male mice the tumour grows either feebly or not at all; but in noncastrated males it grows rapidly because inhibitor is lacking. After a few passages through male mice, secondary alterations become apparent in the granulosa-cells' receiving genes. The cells' sensitivity to inhibitor disappears: they will now grow in females and have become autonomous.

Of the neoplastic diseases of the hæmopoietic and lymphopoietic systems some are autonomous and some conditioned. In the autonomous group there is an increased reproduction rate because inhibitors (which here are present in normal quantities) are acting on injured cells. The injury may affect only some of the cells (*A*) or all of them (*B*). In the conditioned group, on the other hand, there is an increased reproduction-rate because the inhibitors are deficient—the cells being at first unaltered. As the quantity of inhibitor diminishes, multiplication gradually spreads throughout the system (*C*).

A is represented by (among others) Hodgkin's disease. Changes in its aspect are possible when there is increasing disintegration of receiving genes (e.g., the change of Hodgkin's disease into Hodgkin's sarcoma), or when the receiving genes of hitherto intact groups of cells are invaded and injured. In this way smooth transitions from one form of disease into another may arise, for example, lymphosarcoma to acute lymphatic leukæmia.

B is represented by acute lymphatic and myeloid leukæmias and acute erythræmic myelosis (Di Guglielmo's disease).

C is represented by myelomatosis, polycythæmia vera, and chronic leukæmia (both myeloid and lymphatic). The latter diseases are relatively benign, compared with their autonomous analogues, acute erythræmic myelosis and the acute leukæmias.

These concepts will now be applied more specifically to a consideration of the leukæmias.

Inhibitors and the Leukæmias

The concentration of inhibitors in the chronic leukæmias obviously decreases gradually, since patients

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with these diseases have been found to show excessive numbers of leucocytes years before a definite diagnosis could be made. After the initial stages the situation in the chronic leukæmias becomes more complex; this happens sooner in chronic myeloid than in chronic lymphatic leukæmia, the course of which is more protracted.

Because of long-continued shortage of inhibitor, alterations occur in the receiving genes which normally react to it. Such alterations arise gradually in the nuclei of the stem cells, but increase progressively. If the white cells were only immature during the initial stage of the disease, they later become pathologically altered. Thus unchanged juvenile cells and reversibly altered juvenile cells may be seen alongside pathological irreversibly altered cells. Finally more and more of the cells lose their sensitivity completely and the disease enters its terminal acute phase. Working along other lines, Fürth (1953) arrived at a similar conception: "There exist grades of leukæmia, those with seemingly normal cells and those with fully autonomous cells. In some human leukæmias the cells are immature but not altered and may lack autonomy." When radiation has been the cause of chronic leukæmias, in all probability the cells producing the inhibitor have been put out of action.

Much of what has been said so far seems to follow logically from the two assumptions that in multicellular organisms the cells' natural tendency to reproduction is restrained by inhibitors, and that the cells' sensitivity to inhibition is localised in its receiving genes. If these assumptions are correct we should expect that autonomous acute and conditioned chronic leukæmias will prove to differ in both ætiology and character. There are, I believe, strong reasons for thinking that they do.

The *acute leukæmias* are assumed to be caused by any agent capable of injuring the stem cells' nuclei and their receiving genes. Such an agent might be a virus, but its existence in man has not been proved and there are obvious difficulties in proving infectivity. Two pieces of evidence, however, point to an infectious origin.

1. In cattle the infectious nature of acute leukæmia can clearly be seen (Dobberstein et al. 1957, cited by Beyers 1957). The evidence for this is its occurrence in certain areas, its continued existence for a number of years in the same cowsheds, its transmission from contaminated cowsheds to uncontaminated ones, and its disappearance when affected animals are slaughtered.

2. Schwartz et al. (1957) prepared cell-free brain filtrates from patients who had died of acute lymphoblastic, myeloblastic, or monoblastic leukæmia. These filtrates were inoculated into AKR mice—in which leukæmia occurs, but not before the twenty-second week of life. In 71 out of 326 inoculated mice "a wildly proliferating lymphoblastoma occurred, sometimes after only two weeks, but in any case before the 22nd week." Hæmatologists are generally reluctant to admit that this disease was caused by the inoculation, and some say that its emergence was merely precipitated. But nobody has explained how.

Probably most cases of acute leukæmia are caused by virus infection of stem cells; but similar damage can be done by chemicals (such as methylcholanthrene or benzene), or by radiation; so a number of cases of acute leukæmia may have a non-viral genesis.

In the *chronic leukæmias* the situation is quite different; for these diseases can be explained by shortage of inhibitors. Though we shall have no conclusive evidence until the nature of such substances is known, this explanation is supported in two ways—apparently widely different but actually very much alike. These are the improvement produced solely by repeated blood or plasma transfusions, and the changes seen when bone-marrow from patients with chronic myeloid leukæmia is grown in normal human serum. In both cases the explanation lies in the addition of the missing inhibitory factor.

At Leipzig Bürger (1953) treated serious gastric hæmorrhage in a patient with chronic myeloid leukæmia by 26 blood-transfusions, each of 400 ml., over sixty-eight days, and observed a drop in the leucocyte-count from 655,000 to 25,600 per c. mm. Since then chronic leukæmia has been treated at Leipzig with "gehäufte Transfusione"—i.e., accumulated transfusions. It is unfortunate that this treatment is discontinued when remissions have been obtained. Also, better results might be achieved if treatment were initiated earlier, when the disease is in its conditioned phase and the number of autonomous cells is only small. Nevertheless Schulz and Florian (1954) obtained important results in 68 cases (see table). They conclude that restoration of the number of white cells to normal was obtained in about 50% of cases.

TREATMENT OF CHRONIC LEUKÆMIA WITH REPEATED TRANSFUSION

Degree of reduction in leucocyte-count	No. of patients with myeloid leukæmia	No. of patients with lymphatic leukæmia
To normal or almost normal	10 } 44%	15 } 54%
Considerable	2 }	7 }
Small	..	6
None	4 } 56%	12 } 46%
Rise	11 }	1 }
Total	27	41

In these patients the spleen decreases in size, and in some cases the blood-picture and the sternal marrow return to normal. The basal-metabolic rate was measured in 10 patients, and the increased rate was lower in 8 after transfusion.

Plasma-transfusions have effects comparable with blood-transfusions, but washed cells suspended in physiological saline solution have no effect at all; nor have gamma-globulin or dried plasma.

The second piece of supporting evidence comes from the behaviour of chronic myeloid leukæmic bone-marrow cultured in normal human serum. After such an experiment Swaen (1954) reported: "No cells and no types of cells have been seen, which are not also found in 'normal' bone-marrow cultures. In principle this chronic leukæmic bone-marrow behaves like normal bone-marrow." So striking was the likeness that it made him suggest that the pathological cells had died, and that only the remaining normal cells had been studied. But this does not seem very likely, since bone-marrow has been successfully grown even from acute myeloid leukæmia (Israëls 1940).

In comparing the progress of Swaen's culture with that of Israëls', as set out below, one should remember that cells which are not (yet) fully autonomous, have not lost their sensitivity to inhibitors completely. Thus even in the acute leukæmic bone-marrow the normal serum in the culture will inhibit cell reproduction and will give the young elements time to mature. But this maturation does not go so far as in the chronic myeloid leukæmic bone-marrow: "Adult polymorphonuclear leucocytes have not so far been seen in the late cultures; the most mature stage has been the young polymorphonuclear with incompletely separated lobes." (Israëls 1940.)

1ST DAY

Chronic.—The polynuclear cells begin to degenerate; lysis and pyknosis of the nuclei are seen. Large cells having basophilic plasma, without granules, and with relatively large nuclei with a few nucleoli, are present. Apparently these are myeloblasts, which have migrated from the centre of the culture. Mitoses are seen in these cells as well as in the myelocytes and promyelocytes. Some myeloid cells have big granules. Early and ripe eosinophils are present. Moreover, there are a few small cells with pyknotic nuclei, probably lymphocytes.

Acute.—After twenty-four hours embryonic cells are numerous and several show early stages of mitosis. Both early and differentiated myelocytes are present, also in mitosis. Many metamyelocytes and polymorphonuclear cells are phagocytic, although many of the latter are degenerate and fragmented. Monocytes are few and not phagocytic.

2ND DAY

Chronic.—The same picture as before. More degenerate polymorphonuclear cells. Phagocytic cells are seen. The formation of macrophages and migratory cells can be seen.

Acute.—Embryonic cells (hæmocytoblasts and myeloblasts) are still prominent, many in active mitosis. A few monocytes are present, some phagocytotic, and some having red-staining granules. These cells are easily distinguished from the undifferentiated myelocytes, since they have only a few granules, usually limited to a single area in the cytoplasm, whereas the myelocytes have numerous granules scattered uniformly throughout the cell. Metamyelocytes and mature myelocytes are present as before, some of the latter in early mitosis. Many polymorphs are now degenerate.

5TH DAY

Chronic.—Polyblasts are seen, a number of them in mitosis. Moreover there are representatives of the various myeloid cells. The number of mitoses is relatively high.

Acute.—Relatively few embryonic cells, and few mitoses are seen among them. On the other hand, there are many early myelocytes, resembling the myeloblasts, but having small red granules scattered throughout the cell in the characteristic manner. Mature myelocytes are frequent, several in mitosis, and phagocytic metamyelocytes are present as before. Polymorphs are few and mostly degenerate.

9TH DAY

Chronic.—There are probably still a few myeloblasts. More migratory cells and histiocytes. Polymorphonuclear cells are constantly present.

Acute.—Embryonic cells have almost disappeared. Undifferentiated myelocytes are present in fair numbers, some in early mitosis. Many mature myelocytes, including eosinophil and basophil types, are seen. Polymorphs are mostly young forms.

11TH DAY

Chronic.—There are large phagocytic cells. The number of polymorphs is relatively high. Some of them seem degenerate, whilst others are in good condition. A few myelocytes in mitosis are seen.

14TH DAY

Acute.—No embryonic cells are found. Some early myelocytes are present and late stages of mitosis are seen. Mature myelocytes are most numerous and still in active mitosis. Metamyelocytes and young polymorphs are also present.

16TH DAY

Chronic.—Histiocytic elements have increased intensively and prevail in the cultures. A few fine polynuclear giant cells are seen. The culture still contains a small number of polymorphonuclears.

So, after a short period of degeneration in the existing neutrophils, a process of maturing, due to the normal serum, becomes apparent in the white cells in both cultures.

The cells in the " chronic culture ", juvenile through insufficient inhibition, are transformed into mature leucocytes, in relatively high numbers, during the days that follow. Those in the " acute culture ", less sensitive to inhibition, do not reach that stage.

Isolation of Inhibitors

We cannot hope that the particular inhibitory substances which are missing in the chronic leukæmias will be discovered by mere chance. But if, as appears from the evidence I have cited, these leukæmias are benefited by repeated blood-transfusion, and the multiplication of leukæmic cells in culture is inhibited by normal serum, it will be natural to try to find out which serum fraction contains these substances. This, however, is no more than the first step; for we need to isolate the active substances themselves, which might well prove to be prototypes. The use of blood fractions in the treatment of leukæmia has already been tried (Mathé 1957, Rappoport 1957), but only in the acute leukæmias, where, according to my hypothesis, it would necessarily be inadequate. Wasastjerna (1957) is looking for the missing substances in the bone-marrow, but to find them there seems even more difficult than to find them in the blood. Arduous as this latter task may be, it may yet prove the least impracticable way of penetrating the fortress of malignancy. I hope that these few suggestions may excite interest in a trial of appropriate serum fractions for the treatment of the chronic leukæmias—particularly the more serious myeloid form.

Summary

The conventional explanation of malignancy is that unchecked cellular multiplication results from excessive stimulation. An alternative view is that cells have a natural tendency to growth which normally is restrained by inhibitory substances. These may act on a well-defined part of the nucleus (" receiving genes ").

On this hypothesis neoplasia might result (1) from damage to the " receiving genes " (for example, by viruses or X rays) or (2) from deficiency of inhibitory substances. The first cause would give rise to autonomous tumours, and the second to conditioned ones.

When this hypothesis is applied to the leukæmias, acute leukæmia appears to be autonomous and chronic leukæmia conditioned.

Reasons for attributing chronic leukæmia to a deficiency of inhibitory substances include the fall in the leucocyte-count often seen after large transfusions of blood or plasma, and the behaviour of leukæmic bone-marrow in tissue culture.

The possible presence of growth-inhibitory substances in blood requires further investigation of serum fractions, and suggests their trial clinically in chronic leukæmia (especially myeloid).

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" . . . There is in the English character a trait, blent of gallantry and masochism, which admires the overcoming of obstacles above the quality of the results achieved. We like our comedians to be 87 or have a wooden leg; we salute the mother who writes a novel in the intervals of caring for a family of nine; we are enchanted by accounts of surgical operations performed on the high seas with a penknife and by the light of an electric torch. It is not wholly fanciful to see this as at least partly responsible for a popular attitude towards the material deficiencies in the hospital services—' Look what a splendid job our wonderful doctors and nurses are doing with so much against them.' "—NESTA ROBERTS, *The Guardian*, Sept. 14, 1959, p. 8.

Occasional Survey

WHAT IS HEARING?

COMMUNICATION by the spoken word is of the utmost importance to man. Accordingly great effort is made to provide speech to the child born deaf—or, more accurately, born with impaired hearing. Unfortunately, there is still controversy about how this should be done—at what age to start, whether to use a hearing-aid, who should undertake the training, whether to use finger spelling or the oral or aural methods, and whether to put the child in a school for the deaf, a partially-deaf unit, or an ordinary school. A report prepared by Mr. Perry Robinson [1] for the National Deaf Children's Society reflects the multiplicity of ideas about what to do for the deaf, and also shows that on the whole the deaf child is still not taught to communicate freely with his hearing fellows.

What are the reasons for this unsatisfactory state of affairs? The fundamental difficulty is in accepting the fact that "hearing" has to be learnt, and that certain physiological and psychological conditions are essential for this learning process to proceed. Failure or refusal to appreciate this leads to a false conception of the disability imposed by deafness. The disability of deafness is notoriously difficult to understand. Blindness or paralysis is easily imagined, but not deafness: blocking the ears shows how it feels to be cut off from sound, but this does not simulate the experience of the deaf child to whom all sounds are mere noises devoid of meaning. The brain of the deaf child is cut off, not so much from sound, as from all understanding of sound, from nearly all information, and from all except the simplest ideas. Moreover the child, being unable to talk, cannot communicate thoughts and feelings to other people.

LEARNING TO HEAR AND SPEAK

Man acquires experience of the world about him through the five special senses. The information given by sight, touch, taste, and smell is direct, whereas that supplied by hearing is largely indirect and is thought of as words or language or ideas, rather than as hearing. We see an infant grasp an object, look at it, taste it, and smell it, and we realise that he is learning how that object feels, looks, tastes, and smells. We do not so easily realise that at the same time the infant is learning to hear. The infant is not born knowing the meaning of sounds or understanding speech any more than he is born able to talk, but in about a year's time he has begun to have some understanding of what is said to him and to try to produce words himself. The fact that the normal infant has to learn to hear is fundamental to understanding the management of the deaf child. Failure to appreciate this fact is the reason why deaf schools contain so many children who have enough hearing to have acquired speech through hearing.

The changes in the first year of life are so diverse that we should have more than the one word "hearing" to describe the "reflex" hearing of the newborn infant and the "acquired" or "comprehension" hearing of the adult and of the child who has learnt to speak. The reflex hearing of the newborn infant is analogous to that of the lower animals. The primary function of hearing in animals is to give warning of approaching danger: a faint sound will cause an animal to prick its ears and turn towards the source of sound with its muscles tensed; it is poised for flight, and a loud sound will produce flight.

The remains of this primary reflex are evident in the newborn infant, who will jump and blink in response to a loud unaccustomed sound; a sudden loud noise causes an increase in respiratory rate in an infant a few months old. This fear reaction has been seen, too, in dogs, cats, and rabbits; it persists after removal of the entire cerebral cortex, showing that it is a reflex. This reflex hearing is all that is present at birth, even in the infant with "normal" hearing. All sounds when first heard are noises without meaning, just as any new or unfamiliar sound is without meaning to an adult. A foreign language is an unfamiliar sound and is not understood by an adult with normal hearing until he has learnt it. The native tongue of an infant is not understood until he also has learnt it. The ability of the adult to learn a foreign language is, with a few exceptions, pretty poor; and an adult will always have a "foreign" accent because he no longer has the special facility for learning the difference between sounds which is present in the early years of life.

The process of learning starts at birth. Tests of hearing in infants are based on the development of this process. Reflex hearing becomes inhibited as the infant learns to ignore a sound which neither harms him nor does him any good. The infant may not respond at all to a loud bang, or at most he looks up once and then ignores it. With a quieter but new sound the infant will look up or towards the sound once, but not again. To a sound which has been heard dozens of times and always with a pleasant association—his mother's voice, sounds of food, his own rattle—the responses are very different. The child looks in the direction of the sound; changes of expression indicate understanding. The greatest response is to speech. After a time the infant will use his own voice in response, copying first the intonation patterns of the speech around him. Eventually the imitation becomes sufficiently good to be recognised as words, and the infant is said to be talking. Any approximation to a word is received with smiles of pleasure, and the word is repeated in its correct form so that the infant is encouraged to repeat the sound and gradually to perfect his performance.

During all this time the child has been learning to recognise sound and to interpret it. Sounds differ from one another by the different patterns of frequency and intensity of the sound-waves composing them. The brain recognises these differences when they have been heard often enough and loud enough. As a result sensation or perception patterns are imposed on the cells of the cortex. Interpretation is learnt if some one person gives individual attention so that sounds have associations with their meanings. All learning depends on the presence of certain essential conditions. The conditions for learning to hear are that sounds must be heard loud enough, often enough, in association with their meanings, and at the right age—the first months and years of life when the infant has a special facility for learning to hear.

THE "SOUND DEPRIVED"

The child born with impaired hearing fails to develop spontaneous speech, not because the brain is unable to learn the recognition and interpretation of sounds, but because sound impulses do not reach the cortex loud enough or often enough. These children are "sound deprived". Other causes of sound deprivation will delay

1. Report for the National Deaf Children's Society on the Care of the Deaf. By J. B. Perry Robinson. Published by the National Deaf Children's Society, 1 Macklin Street, London, W.C.2. Pp. 96. 5s.

or prevent the development of speech. Infants in residential institutions talk late because of the lack of individual attention; neglected children may fail to talk at all, and may show absolutely no response to sound at first testing. This neglect is not always vicious. Sometimes it is due to the fact that the parents suspect deafness and cease talking to the infant because they feel it is useless. They may, however, be continually testing the infant with loud noises—banging trays and so on. This rapidly causes inhibition of response, and the infant may simulate extreme deafness. When individual attention is paid to children and they are given sounds to hear they rapidly develop the learning process. Deaf children will do the same if sounds are brought within range. Some parents discover this for themselves and always speak close to the child's ear. A hearing-aid is obviously more convenient and increases the range at which the infant can hear.

The hearing of the deaf child is often classified according to whether he (*a*) can hear and understand speech, or (*b*) cannot hear and understand speech. The conclusion is then made that the second group of children will never be able to understand speech through hearing. This disregards the learning process and the fact that the infant with " normal hearing " is not born understanding speech any more than he is born talking. The deaf child must be given comparable listening opportunities before he is written off as having too little hearing to be able to learn to hear and understand speech. The normal infant has been listening for about a year before he produces his first attempts at words, and it is unreasonable to expect the deaf child to manage with a shorter period of listening. In fact almost all deaf children have hearing which can be developed and used for the acquisition of speech provided they are given the opportunity to listen early enough, during the important early years. With each successive year of age the problem becomes more difficult. When the process of learning to hear has become common knowledge, parents will suspect deafness and will not be told by doctors to bring the child back at three or even five years because " it is impossible to test the hearing earlier ".

PROMOTION OF HEARING AND SPEECH

As soon as impairment of hearing is diagnosed the parents must be instructed about the process of learning to hear so that they can know how to help their child. Only they can give the infant the individual attention that is essential. Every mother can give this attention provided her role is explained to her and she is seen from time to time to deal with snags and to remind her of the principles of learning to hear. The provision of a home help may make all the difference, and is every bit as necessary and reasonable as in cases of disability from other causes. Hearing and speech centres should be provided more widely with peripatetic teachers for outlying areas. In the meantime transport should be provided to bring the infant and parents to the existing centres as often as is necessary.

Financial provision must also be made for the immediate supply of a suitable hearing-aid with high-fidelity reproduction and a high degree of amplification. Automatic volume control is necessary, and the aid must be a monopack of robust construction with a metal case and leads that do not pull out or break easily. A second aid should be available when repairs are necessary.

The acquisition of speech is not something that can be allowed to drag on all through the school years. The normal infant learns to speak before he goes to school to start his education. The acquisition of speech is an essential preliminary to education. The child develops power of thought and acquires information all through school life, but before he goes to school he has already acquired a basic vocabulary and knowledge of the way that words are put together to form the " propositions " which Hughlings Jackson described as the units of speech. The deaf child must be given the opportunities to develop the same basic equipment of speech as the hearing child during the early years when the physiological and psychological facility for learning to discriminate between sounds is present. It does not matter that the sounds he hears are different from those the rest of us hear. What matters is that he should have a code of sound signals associated with their meanings. He will still be deaf, but his disability will be comparable to the lesser disability of acquired deafness.

EDITH WHETNALL.

Conferences

LAURENTIAN HORMONE CONFERENCE

FROM A CORRESPONDENT

AT this meeting, held at Mont Tremblant from Aug. 30 to Sept. 4, primary consideration was given to the mechanism of hormone action.

The observation that catalytic and therefore physiological concentrations of the natural œstrogens catalyse the action of *iso*-citric acid dehydrogenase has been extended to embrace all triphosphopyridine nucleotide (T.P.N.) sensitive dehydrogenases; in this way key metabolites of the Krebs citric-acid cycle and the important glucose-6-phosphate shunt could be involved in the release of biological energy for cell growth. It is of secondary importance [1] that the precise mechanism of action of the enzyme is still in dispute, for progress in other directions has re-emphasised the importance of the link between steroids and the adenosine dinucleotides. Chemical affinity of the adenosine molecule for steroids has been shown to be influenced by structural and steric features of the steroid moiety, and this association of steroid hormone and nucleoside may be linked with the role of the pyridine nucleotides (which contain the adenosine molecule) in steroid-sensitive dehydrogenase systems. Weber [2] has shown that energy absorbed by the adenosine of dihydrodiphospho-pyridine nucleotide is transferred to the nicotinamide radical which is the site of reduction of the co-enzyme.

It seems probable that corticotrophin acts on adrenal tissue through the medium of a heat-stable compound 3′ : 5′-cyclo adenylic acid (3′ : 5′-A.M.P.) which accumulates during corticotrophic stimulation. Both corticotrophin and 3′ : 5′-A.M.P. increase phosphorylase activity of adrenal tissue and stimulate steroid biogenesis. An enzyme which forms 3′ : 5′-A.M.P. from adenylic acid is widely distributed in tissues of all phylla, and there is apparently a close analogy between the action of corticotrophin on adrenal tissue and of adrenaline or glucagon on liver, as all seem to be mediated through 3′ : 5′-A.M.P.; they differ only in the nature of the tropic hormone activating the target organ.

Peptide Hormones

The availability of monkey pituitary as a consequence of the production of Salk poliomyelitis vaccine, and of

1. Villee, C. *Ann. N.Y. Acad. Sci.* 1959, **75**, 524.
2. Weber, G. *Nature, Lond.* 1957, **180**, 1409.

human pituitaries following hypophysectomy for carcinoma of the breast, has enabled a sensitive method to be developed for the serological determination of growth hormone in the plasma of primates. Earlier failure to obtain sera antigenic to growth hormone is now explained by the absence of cross-reaction between human-growth-hormone antibody and growth hormone of all species except monkeys and possibly fish. Human pituitary growth hormone (prepared by Raben) on repeated injection led to a high antibody titre which showed little or no cross-reaction with other human pituitary hormones. Assay is based upon the hæmagglutination of sheep erythrocytes conditioned by tannic acid to absorb growth hormone against serial dilutions of growth-hormone-antibody serum. Applied to human plasma and to fluids containing low concentrations of growth hormone, the method is most sensitive when used indirectly to determine how much growth-hormone antiserum is necessary to inhibit hæmagglutination. Application of the method has shown high plasma levels of growth hormone in acromegaly and abnormally low values in hypopituitarism. The mean level before puberty is above that in adults. Intravenous injection of growth hormone was more effective than intramuscular injection in establishing and maintaining high levels of growth hormone.

New Polypeptides

For some time it has been clear that erythropoiesis is under humoral control. A new method of assay based upon the rate of appearance of radioactive ^{59}Fe in the blood of polycythæmic rats has led to the preparation of the highly purified polypeptide hormone—erythropoietin.[3] Bilateral nephrectomy but not bilateral ligation of the ureters prevented the secretion of the hormone, and as the removal of other organs was without effect on secretion erythropoietin is probably formed exclusively in the kidney. The site of action appears to be the spleen, but this is less certain. The number of circulating erythrocytes is reduced by hypophysectomy, by hyperoxia, by starvation, or by phenylhydrazine poisoning; injection of cobaltous chloride mimics the action of the hormone stimulating the early stages of maturation and releasing red blood-cells into circulation. Erythropoietin levels fall at high altitude or following blood-transfusion. The determination of the hormone at levels found in normal plasma is difficult; but in multiple myeloma, Hodgkin's disease, leukæmia, and anaplastic anæmia levels were much higher than normal. The response in pernicious anæmia was variable, possibly owing to the inadequacy of the marrow. On a preparative scale repeated chromatography on ion-exchange resins has given a highly purified active polypeptide with a molecular weight of about 40,000. This material appears to be electrophoretically pure, and in aminoacid composition closely resembles α_1-lipoprotein. The material is reasonably heat-stable but is completely inactivated by proteolysis.

The list of biologically active polypeptides is expanding. Incubation of plasma or of some of its protein components with proteolytic enzymes appears to liberate a wide selection of polypeptides which pharmacologically resemble the neurohypophyseal hormones.

Thyroid Hormone

Using the bioassay method based on the uptake of ^{131}I in the chick, further purification of the thyrotropic principle has been achieved. Transferable thyrotropic mouse tumours provided a richer source of the hormone than desiccated pituitary and were not contaminated with other pituitary hormones. Again, chromatography on ion-exchange resins, especially on the cation exchanger diethyl amino ethyl cellulose (D.E.A.E.), suggests that there may be more than one active compound. Chromatographically distinct fractions assaying 20–800 units per mg. were electrophoretically homogeneous with molecular weights ranging from 20,000 to 30,000. On analysis, the aminoacid content accounted for less than 70% of the molecule, which contains both galactosamine and glucosamine.

3. Jacobson, L. O., Goldwasser, E., Gurney, C. W., Freed, W., Plzak, L. *Ann. N.Y. Acad. Sci.* 1959, **77**, 551.

Hormones and Metabolism

The food consumption of animals in relation to ambient temperature suggests that the difficulty of heat dissipation may be a powerful factor in the control of food intake. There is some evidence of a regulatory centre at hypothalamic level, but the nature of the mechanism and the character of the hormone (if there is humoral control) is unknown. It has been suggested that plasma and depot fat have a dynamic role, and that metabolic changes take place at the site of deposition. Details of these metabolic changes have yet to be revealed, but evidence points to adrenal involvement.

Public Health

Syringes for Immunisation Injections

IN his annual report for 1958, Dr. C. Metcalfe Brown, medical officer of health for Manchester, describes a unit for dry sterilisation of syringes and needles used for immunisation injections. The Manchester health department is believed to be the only one in the country providing a complete system of dry sterilisation for this purpose.

The unit, which was established in April, 1957, is accommodated in the department's cleansing and disinfecting station. One of the two sections deals with the reception of used syringes and needles and the cleansing and drying processes; the other section deals with assembly, sterilising, and packing. A trained nurse is in charge, and she is assisted by five female attendants; all the staff are required to work also in the cleansing and disinfecting unit when necessary.

The basic stock consists of 10,000 Luer-type, interchangeable, 1 ml. syringes and 500 Luer-type, interchangeable, 10 ml. syringes, with aluminium containers. The smaller syringes are used for injections given in the prophylaxis of diphtheria, whooping-cough, and poliomyelitis, whilst the larger ones are used for taking blood samples from mothers and children attending maternity and child-welfare centres. A separate sterile syringe and needle is used for each inoculation. 80,500 sterile outfits were prepared and issued in 1958.

Technique of Sterilisation

When the syringe and needle outfits are received at the unit, after use, they are all inspected for breakages; then the component parts and the metal containers are steeped in a sink of hot, weak, green soft-soap solution for ten minutes. Afterwards they are transferred to an adjoining sink and rinsed thoroughly by means of a special rinser attached to a hot-water supply.

All parts are collected on flat trays and dried in an electrically heated oven for one hour at a temperature of 80°C. Reassembly takes place after needles have been inspected for sharpness and the plungers of the syringes have been smeared with a little silicone fluid to prevent sticking in the barrels.

Each syringe, complete with needle and stillet, is placed in a metal container with a small piece of cotton-wool inside the cap for use as a sterile swab. The filled containers are placed in wire baskets ready for conveyance to the hot-air steriliser in the second room of the unit.

Six baskets, each holding 72 syringe and needle outfits, are placed in the steriliser and heated at a temperature of 160°C for $1^1/_2$ hours; they are then removed from the steriliser and cooled.

After cooling, each metal container is sealed with ' Sellotape ' at the junction of the cap and the body and labelled " sterile."

Outfits are packed in specially designed wooden boxes, of various sizes, for distribution to clinics.

In England Now

A Running Commentary by Peripatetic Correspondents

IT was nice to see old "Shonnie" again while doing the routine round of the harbour of "Portrona". With the burden of many years his step had lost some of its vigour but the warmth and sincerity of his greeting was unabated. Our crack turned inevitably to matters of health and I was reminded of his great worry and sore trial on my last visit.

A powerful brand of very black twist had been his smoke over the years and how he loved it! Then one day he found he could not identify the fishing-boats so easily and his Bible suddenly became dim. So on the next visit of the "Eye Professor" from "Inbhir-nis" he would get stronger glasses for his dimming eyes. To his horror he was given the choice between stopping smoking and going blind.

The verdict was accepted with Christian patience and fortitude but obh! obh! his temptation was great. He struggled for days and in a desperate attempt at solace he consulted his Elder. "Uilleam Aonghais Beag" would have listened patiently to the tale of woe. I have no doubt the solution was eventually offered after prayer and meditation, for their faith is profound and simple. It was that possibly "Shonnie" could have a small smoke once or twice a day provided he kept his eyes shut while smoking.

Whether "Shonnie" kept his eyes shut and had his smoke I do not know, but he is a non-smoker now. If he cannot identify the fishing-boats as they come round the lighthouse, he can as they come round the island, and his Bible is as bright and joyous as ever.

* * *

After dinner someone told us of a spoof radio programme, broadcast early one April, about the spaghetti-picking festival in Southern Italy, when the spaghetti is plucked from the trees and there are accompanying ceremonies and celebrations—all described in detail. It seems that many people fell for this absurd tale and took it seriously; we all thought that an excellent joke. When we had done laughing at those gullible folk, our host asked, "But seriously, have you ever thought how they get the hole down the middle of the spaghetti?"

At this we all fell to suggesting means of making the holes, and much learning and ingenuity were exhibited. The mechanically-minded among us proposed machines and processes that might succeed, and others spoke of the malleability, ductility, cohesiveness, and surface tension that would be needed in the pasta, and of the application of Poiseuille's formula to air passing along the hole as it expanded when the spaghetti was cooked. I (who have little physics but am something of a wag) suggested that they might make the hole first and then spray the pasta on to it.

In the cooler atmosphere of the next morning I began to wonder whether spaghetti actually does have a hole down the middle. Next time I have some I shall look; and if it doesn't I shall be very cross with our host for deceiving us with such a silly pointless question.

* * *

Now that, after an interval of several years, there is a new baby in the family, I find myself much better able to deal sympathetically and effectively with feeding and other problems of infancy. It would seem that it is not enough for a doctor to have a family of his own: to maintain his efficiency he must keep adding to it at regular intervals. Should the Post-Graduate Education Committee consider offering special family allowances to doctors as an alternative to formal courses in infant welfare?

* * *

For years a major source of irritation on Monday mornings has been the inability of my colleague, Dr. X, to arrive in time for the clinic. As a result I always have to do most of his work as well as my own. "I wish you could think of a way to get me out of bed," he often says.

A minor source of irritation on Monday mornings has been the regular arrival of a registered letter from a mental patient, long since discharged. But of late my small son has taken charge of this, for he loves to run downstairs in his pyjamas in answer to the postman's knock, and signing the counterfoil makes him feel important. A fortnight ago he went to boarding-school. When I found that I had to roll out of bed myself to deal with the registered letters, Monday morning became quite intolerable. Something had to be done.

Now I have solved both my problems at one brilliant stroke of the pen. I wrote to the patient the following letter:

"Dear Mrs. Y, I am afraid that circumstances have changed and it will not be possible for me to receive your letters in the future. I have accordingly arranged for them to be received by Dr. X at the following address . . ."

My colleague had a sour expression on his face when he arrived on Monday, just as the clinic was starting. I haven't yet dared to ask him whether the patient mentioned my name, but I think he has his suspicions.

* * *

When the steel trunk in the garage began to show signs of bursting at the seams and every available cubic foot in the loft had been filled we realised that the time had come to dispose of some of our old medical journals. My husband was for attacking the *Lancets*, arguing that I did not refer to them half as often as he did to his special journal (whose solid sleekness I have always vaguely resented); and when I protested vehemently he added that I could always go to a library if I really wanted to look up anything, instead of sitting for hours on the floor of the garage. I refrained from pointing out his inconsistency, but I must have looked a little hurt, because he next suggested more kindly that I give my *Lancets* to some needy institution, such as my present hospital, and then I could look at them whenever I liked.

Somehow I could not convince him either of the difficulties attending my researches or of the importance of my *magnum opus*. For years I have been working on an indexing system which will enable me to find at a moment's notice any peripatetic note for which I happen to be in the mood.

* * *

SORE POINTS

Freckles and warts
Of various sorts
And corns and callouses
And numerous bruises
Occasional lumps
Inconvenient bumps—
  It's just the little injuries I find
  A trifle ugly and unkind.

There is prickly heat
And there's toes and there's feet
And a sensitive rash
Forbids me to wash
While an irritant patch
Compels me to scratch—
  Perpetual rubs like these begin
  To make one feel a martyr to one's skin.

Rubor and dolor
Beneath a stiff collar
A furtive papilla
Inside the axilla
Or calor and sudor
In regions still ruder—
  I ask you, is it really loyal
  This tendency of yours to grow a boil?

You're so quick to reveal
What I'd rather conceal;
Though there's nothing between us
Your betrayals demean us—
You'll be telling 'em next
We're incompatibly sexed:
  I tell you once for all, dear Skin,
  At times my gratitude wears thin.

Letters to the Editor

IMIPRAMINE

SIR,—In my opinion, unpopular though it is in these days of acts of faith in the technique of medical statistics, "qualitative" pilot-studies, based on the clinical observation of relatively small numbers of patients, may—anyhow, in the first instance—provide as much reliable information as later large-scale assessments.

Some two years ago, I was invited to conduct such a trial of N (γ-dimethylaminopropyl)-iminodibenzyl hydrochloride—now marketed as 'Tofranil' and officially known as imipramine—in the treatment of depressive syndromes. Pioneer work with the drug in injectable forms had already been done on the Continent, with favourable results. But, because of the large volume needed for injection and because I wished to use the drug on ambulatory patients, I was unwilling to try it until it could be taken by mouth. Since this became possible early last year I have prescribed the drug for 45 private patients suffering from depression, mostly with striking symptomatic improvement.

Most accounts of the use of imipramine come from Switzerland and Canada.

Kielholz and Battegay [1] reported improvement-rates of 50% in outpatients, and 67% in inpatients. Kuhn [2 3] states that 75–80% of depressive patients respond to the drug—even some patients resistant to electroplexy. Azima and Vispo [4] came to the conclusion that imipramine is a long-term remedy, since stopping it after four to eight weeks is likely to result in a return of depressive symptoms within a week. In his short survey, Grünthal [5] says that tests on healthy persons established its special effect on affective experience. Unlike chlorpromazine and reserpine, it did not lessen drive and initiative. Straker [6] regards it as the most promising drug ever to appear for the relief of depression. Of 70 patients reported on by Mann and Macpherson,[7] 63% were much improved or recovered. These workers were concerned, however, over the side-effects and other possible reactions.

In my own series the method of selection was imprecise, but included one or more of the following criteria: (1) there were reasons which made it desirable to avoid electroplexy (E.C.T.), if possible; (2) E.C.T. in the past had failed to resolve depressive attacks satisfactorily; (3) anxiety and tension were features of the total depressive syndrome; (4) drugs of the amphetamine group had failed to bring about a symptomatic improvement; (5) various "tranquillisers" of the promazine group, prescribed by other practitioners, had been unsuccessful.

Patients were asked to report any side-effects (subjective or objective), and to tell me fortnightly how they were getting on. Their instructions on dosage were:

1. Treatment should begin with 4 tablets on the first day.
2. During the next four days the total number of tablets per day should be increased to 10.
3. This dosage should be maintained until clinical improvement is seen, when it may be reduced to 2–6 tablets per day.
4. On an average, full clinical improvement is apparent between the tenth and fourteenth day.
5. It is advisable to divide the daily dose into three smaller doses.

Of my 48 patients 18 defaulted in various ways—either they refused to take the drug after the first day or two, or they were so severely disturbed that they required immediate E.C.T. or admission to a mental hospital outside my control; or else they failed to keep in touch with me, in spite of their promise to do so. Thus the results could be assessed in only 30.

There were 24 "successes", 3 "partial successes", and 3 "failures". The criterion for "success" was the resolution of depressive symptoms soon after beginning to take the drug (usually after a fortnight on the full dose) as fully as could be expected with a full course of modified E.C.T.—but without the memory disturbance, of course. "Partial successes" comprised patients who responded well but incompletely to the drug, and/or who required E.C.T. in addition. Of this latter group, I had the definite impression that they responded better to E.C.T. (with, for the most part, fewer treatments) than they would have done without imipramine. I was often able to judge this, because many of these patients had been treated by E.C.T. during previous attacks.

The following are two typical successful case-histories:

CASE 1.—Mrs. A, aged 48 in 1958. Had a history of endogenous depressive psychosis and also of remitted disseminated sclerosis. I gave her several full courses of E.C.T. over the years, always with satisfactory, but often delayed, response. On the last occasion, she required only 4 treatments by E.C.T., apparently because she was taking imipramine at the same time. The chief side-effect on the full dose was staggering gait—a very frequent complication in my experience. She was able to reduce the dose to 4 dragées a day and to cut them out altogether after six months. She has remained depression-free ever since.

CASE 2.—Mr. B. First seen in 1951, when he was aged 50. Diagnosis: early involutional depressive psychosis. He had always been nervous and highly strung. Was originally treated at Belmont Hospital for nine weeks with modified insulin and stilbœstrol. Treated from May to August, 1951, at the Maudsley Hospital, where he was given 6 treatments by E.C.T. His depressive syndrome returned after an operation for hernia in 1957, and in 1958 he required a full course of modified E.C.T. with me (10 treatments in all), with excellent results. He started imipramine in September, 1958, and experienced many side-effects. On Oct. 17 he was still taking 10 dragées a day. He was complaining of innumerable hypochondriacal symptoms, but was definitely depression-free in the clinical sense. The following telephone message was received on Oct. 22: "when I came to see the doctor on the 17th, I was like death warmed up. On the way out, your butler said—'you are a hundred per cent. now, Sir'. After ten minutes in the car being driven by a chauffeur, I suddenly decided to drive myself, and drove the whole way home. I have now lost all my ills and chills. Had an enjoyable day with friends. Nothing is definitely settled yet with regard to my business future; but my family doctor is signing me off on Monday." He had 600 dragées in all.

In my series side-effects were less troublesome than with chlopromazine. Dryness of the mouth is the commonest, and a few patients had disturbance of visual accommodation, skin eruptions, or dizziness. Other possible side-effects which have been reported in isolated instances are tremor (which may be mild or gross [8]); sweating; slight temporary tachycardia; coldness in hands, feet, and nose; œdema of the eyelids; and loss of desire to smoke. In none of my cases did the side-effects persist after discontinuing treatment. Rashes may usually be controlled, without stopping the drug, by simultaneous administration of an anti-histamine.

Like most of the authors I have cited, I see strong indications that imipramine is a most useful drug in the treatment of depressive psychosis—especially endogenous

1. Kielholz, P., Battegay, R. *Schweiz. med. Wschr.* 1958, **88**, 763.
2. Kuhn, R. *ibid.* 1957, **87**, 1135.
3. Kuhn, R. *Amer. J. Psychiat.* 1958, **115**, 459.
4. Azima, H., Vispo, R. A. *ibid.* p. 245.
5. Grünthal, E. *Psychiat. et Neurol, Basle*, 1958, **136**, 402.
6. Straker, M. *Canad. med. Ass. J.* 1959, **80**, 546.
7. Mann. A. M., Macpherson, A. S. *Canad. psychiat. Ass. J.* 1959, **4**, 38.
8. English, H. L. *Lancet*, 1959, i, 1231.

depressive psychosis. Further large-scale trials, involving statistical analysis, comparison with control groups, and the use of the " blind " and " double-blind " techniques, are called for.

My thanks are due to Dr. Alan Broadhurst, Messrs. Geigy's chief medical officer in this country, for inviting me to conduct this clinical trial.

London, W.1. E. B. STRAUSS.

SIR,—The considerable promise, both clinical and theoretical, of imipramine (' Tofranil ') as a therapeutic agent in depressions, prompts me to comment on the letter of Dr. Fullerton and Dr. Boardman (June 6) although my experience with the drug has been limited.

During the past two years, I have sporadically had occasion to use G22355, which was the provisional label for the new compound. In my cases some of the side-effects listed by Dr. Fullerton and Dr. Boardman—namely, restlessness, tachycardia with palpitation, and insomnia occurred regularly. In controlling these, chlorpromazine, which by itself is, of course, counterindicated in states of depression, proved invariably effective in doses of up to 150 mg. a day. A patient in a melancholic near-stupor improved markedly on such combined regimen within a few days.

Azima [1] also makes use, at least in a proportion of his cases, of a combination of imipramine and chlorpromazine. Alternatively, he recommends sodium amylobarbitone for the control of excitement. Both he and Kuhn [2] before him, who have studied many cases, have noted that these side-effects, and others which have been fully described in their publications and which I too have met, subside spontaneously or soon decrease with the dosage of the drug remaining at the optimum level. This stands, of course, in contrast to amphetamine medication which Dr. Fullerton and Dr. Boardman mention as a comparison with imipramine.

Their conclusion that imipramine acts as a central stimulant must be challenged. However the side-effects are brought about (centrally and/or peripherally)—and this applies also to the amphetamines whose mode of action has been by no means fully elucidated—the therapeutic effect of imipramine ought to be regarded as a thing apart. A chemotherapeutic agent favourably influencing neurotic and psychotic depression within the setting of a clear sensorium merits the hypothesis that it acts on the biochemical processes underlying guilt phenomena and the various manifestations of self-aggression.

It has been my distinct impression in cases of schizophrenia treated with the phenothiazines that whenever the treatment gives favourable results they occur by virtue of a decrease in anxiety, permitting a spontaneous healing process to set in. In the study of the biochemical processes underlying anxiety, the fact of its response to the phenothiazines might provide a valuable clue. Analogously, experiences with imipramine in depressions may in time help to elucidate the physiology of guilt and self-aggression. Similar views have been expressed by others.[1–3]

My thanks are due to Dr. Alan Broadhurst, of Geigy Pharmaceutical Co. Ltd., who supplied the imipramine.

London, W.1. JOSEPH ZELMANOWITS.

SIR,—In recent months there has been much interest in the side-effects of imipramine (' Tofranil ') which is now being used on a fairly large scale in this country. I would like to draw attention to an unpleasant side-effect which I have not seen described before.

A married woman, aged 33, suffered an attack of mania when 17 years old. This has been followed by attacks of endogenous depression, lasting 8–10 days, recurring every 6–8 weeks. It was decided to treat her with imipramine. On the 1st day she received 75 mg. intramuscularly. This was increased by 25 mg. daily till on the 6th day she received 200 mg. intramuscularly. On the 7th day she received 150 mg. intramuscularly plus 100 mg. orally. On the 8th day she received 100 mg. intramuscularly and 200 mg. orally. On the 9th day she received 300 mg. orally. For the next 3 days she received 225 mg. orally, and the drug was then stopped as her depression had resolved. On the last (12th) day the patient complained of a tingling in her fingers, and a fine tremor of the fingers was noticed. She also complained of a " jumping in her jaw " which she said interfered with her speech. She held her jaw in an attempt to steady it. Inspection revealed an upward symmetrical twitch of the upper lip occurring every 5–15 seconds, uninfluenced by over-breathing or Chvostek's manœuvre. In addition there was a less frequent jerking of the lower jaw, usually towards closure, but occasionally in the reverse direction, occurring every 2 or 3 minutes.

All these symptoms disappeared within 3 days after cessation of the drug. By this time the patient had swung into a mild mania and was readmitted 6 days after cessation of imipramine.

She was treated with chlorpromazine which was increased daily to 150 mg. q.d.s. orally 11 days after the cessation of imipramine. On that day there was a reappearance of the upward twitch of the upper lip (but not of the paræsthesiæ in the fingers, tremor, or jaw twitch) occurring once per minute. The chlorpromazine was reduced to 100 mg. t.d.s. orally, and the symptoms disappeared.

It would appear therefore that the twitching of the upper lip was potentiated by chlorpromazine given 11 days after the cessation of imipramine.

The paræsthesiæ in the fingers and fine tremor thereof have been frequently noted in patients receiving 200 mg. or more per day of imipramine, but have never been sufficient to interfere with treatment.

Whether the appearance of frank mania after 16 years of solely depressive phases can be attributed to a delayed effect of imipramine must remain an open question.

Department of Psychiatry,
Royal Infirmary,
Manchester, 13. N. L. GITTLESON.

1. Azima, H. *J. Canad. med. Ass.* 1959, **80**, 535.
2. Kuhn, R. *Schweiz. med. Wschr.* 1957, **87**, 1135.
3. Azima, H., Ogle, W. *J. Canad. med. Ass.* 1954, **71**, 116.

DIMINISHED RESPONSIBILITY

SIR,—I dreamed that I overheard this dialogue:

SOCRATES: What are you discussing so heatedly?

APOLLODORUS: A learned and thoughtful physician has suggested that the legal doctrine of diminished responsibility be done away with.

SOCRATES: What are his reasons?

APOLLODORUS: They are three, Socrates; but we were discussing particularly the first, which is his acceptance of determinism. He holds that the phrase " free will " is based on illusion, and that human behaviour is determined by constitution and nurture.

SOCRATES: What is his evidence for this determinism?

ANALYTICUS: That clinical experience, especially in psychoanalysis, shows that when choices are offered as to conduct, the path taken is determined by personality structure.

SOCRATES: Are all men now agreed on this interpretation of psychoanalytic findings?

ANALYTICUS: No, Socrates; but the physician believes that more men will agree.

SOCRATES: Now if all men agree in accepting determinism, is it not wrong to punish a criminal at all? For if his activities are determined by blind forces and he has no free will, he cannot choose not to commit a crime; in which case it is unjust to punish him, and the threat of punishment will not deter men from criminal acts.

APOLLODORUS: It would seem so, Socrates.

SOCRATES: If the doctrine of determinism is true, does it apply only to criminals?

ANALYTICUS: Of course not.

SOCRATES: Does it apply to all men equally?

ANALYTICUS: Certainly.

SOCRATES: Then it must apply to those who make and administer the laws, and indeed to the learned and thoughtful physician himself, and to us talking here.

APOLLODORUS: Yes.

SOCRATES: Then if determinism is a true doctrine, those who make and administer the laws and those who argue about them can no more control their words and deeds that can the man they would—or would not—punish.

APOLLODORUS: That is true.

SOCRATES: It seems, then, that if free will is not an illusion, men must be held in some part accountable for their actions; and if free will is an illusion, it is equally an illusion that we have any choice in the making and administration of laws; in other words, the lawmakers are as free of responsibility as is the criminal.

Boston, Mass. D. M. JACKSON.

POTASSIUM-SECRETING TUMOURS OF THE LARGE INTESTINE

SIR,—It seems to us that Dr. Abbott and his colleagues (Sept. 5) have misconceived the problem of villous tumours of the colon and rectum. The quantity of electrolytes in the stools of patients with ulcerative colitis, cholera, &c., is not relevant. The patient with a villous tumour passes fæces which are normally formed and, in addition, a large quantity of clear viscid or watery fluid which has originated in the tumour. The rest of the colon is quite normal and there is no intestinal hurry. The interesting fact is that this fluid contains a concentration of potassium which may be from four to sixteen times that of plasma, implying an active secretion by the tumour cells.

There is, of course, loss of water and other electrolytes, which plays its part in the ultimate collapse, but it seems to us that it is the active secretion of potassium which is interesting.

Western Infirmary, Glasgow. A. D. ROY.
Radcliffe Infirmary, Oxford. H. ELLIS.

A COLLEGE OF PATHOLOGISTS

SIR,—Dr. Cornes (Sept. 5) is quite right. A College of Pathologists could do nothing but good. Even Peter Davey admits that it would be good for pathologists. His objection to the scheme is the fear that it would lead to three colleges today, four tomorrow, and every man his own college the day after. This fear I believe to be groundless. If the psychiatrists wish to follow the pathologists, then good luck to them. Their claims to autonomy are nearly as good as ours. After them, however, I foresee no rush. The cardiologists, for instance, and the thoracic surgeons, appear to be perfectly happy in their respective homes. Furthermore, as the pathologists are now finding out, the act of partition requires a lot of people, a lot of money, and a lot of very good reasons.

Too much has been made in this controversy of the word "splinter". The tree of British medicine was chopped up long ago and nothing can put it together again. The only question now is what size the logs should be. This being so, it is surely better to have more homogeneous units, such as the Royal College of Obstetricians and Gynæcologists, than, in the name of a quite spurious unity, to cram all specialties into the present organisations whether they fit comfortably or not. In Glasgow it appears that local loyalties are strong enough to weld together all branches of the profession. In London they are emphatically not. The two larger colleges uncomfortably resemble the Transport and General Workers Union. Since, as Peter Davey says, monolithic unity is no longer possible it may well be that further separation would lead to a greater unity of function. If multiplicity reduced the influence of the individual colleges, they would be forced to act more frequently in concert. At the moment the P.R.C.P. is accepted more than any other man as the spokesman of the profession. It is of great importance that there should be someone in this position; but it is a bad thing that he should always be a physician, elected by a comparatively small band of self-chosen colleagues. Too often, after past P.R.C.P.S have spoken, there have been murmurs in the backwoods "We was robbed".

There is a simple way to guard against this situation. Take all the Colleges and Faculties of England and Scotland. Add the pathologists and perhaps the psychiatrists. Throw in, if you will, one or two more for luck. Then make it known that if one man is to speak for the profession, it should be the chairman of the Committee of Presidents. The thought that the chairman might be a pathologist will doubtless be greeted with a fine lack of enthusiasm; but just consider—one day a general practitioner might even say for us what most doctors were really thinking.

At present, pathologists are not a very happy breed. We have no spiritual home and far too little corporate morale. We are neither physicians nor surgeons, and most of us are certain that, however much hospitality may be offered us by the senior colleges, we will never feel really happy in either of them, and we will never really belong. But we are sufficiently numerous, and strong enough, to stand alone. And as a corporate body we would have much to offer the profession and the world. Most of us feel, as a recent survey has shown, that the time has come to take another chop at the medical tree and to say with pride "This splendid log is Pathology".

German Hospital, London, E.8. J. A. U. MORGAN.

EARLY DIAGNOSIS OF PREGNANCY

SIR,—I was interested to read Dr. Forster's letter (Aug. 29) on the early diagnosis of pregnancy using 'Disecron'. Dr. G. D. Matthew, of the University Department of Obstetrics and Gynæcology and I also found that the "withdrawal bleeding test" had a high degree of accuracy in a series of 104 patients with secondary amenorrhœa. Whether it is desirable to use this method as an alternative to the Hogben test is, however, very doubtful.

Since 1947 we have done more than 250,000 Hogben tests in this laboratory, with an accuracy of 99·3%. The majority of these tests were done with urines collected 10–14 days after the missed but expected period. The results of the tests are available within 24–48 hours after the arrival of the urine in the laboratory, with the exception of specimens received at the weekend. About 4 oz. of urine is required, and if this is sent in a polyethylene bottle the specimen is certain to arrive intact.

Even though the use of disecron might be more convenient for some general practitioners, there can be very few people who, when given the alternative of collecting a specimen of urine or of receiving two intramuscular injections, would choose the discomfort of the latter. The most important objection to a pregnancy test involving the injection of steroid material when other adequate tests are available is that we cannot be certain that the resulting hormonal imbalance, however small, may not itself cause an abortion in susceptible women.

Pregnancy Diagnosis Laboratory, Usher Institute, Warrender Park Road, Edinburgh. B. M. HOBSON, Scientific director.

SIR,—Whilst I agree in principle with Dr. Forster, it appears that an important reason for use of hormones in pregnancy diagnosis is that it requires less of the general practitioner's time than injections or urinary gonadotrophin tests.

I have found that diagnosis of pregnancy in the early stages —i.e., after the first missed period—is completely accurate when a course of four tablets of combined norethisterone 10 mg. with 0·05 mg. ethinylœstradiol ('Primodos') is taken

—one tablet night and morning on each of two consecutive days. This produces either withdrawal bleeding (no pregnancy) or no bleeding (indicating pregnancy) within 3–6 days. In 23 cases during the past year this method has proved completely accurate, and the cost to the N.H.S. compares favourably with that of gonadotrophin tests.

Glasgow. R. J. KENTON.

VARICOSE VEINS

SIR,—I cannot let pass without comment Surgeon Captain Cleave's fascinating contribution of Aug. 22.

His explanation in regard to the sluggish and overloaded colon resulting from low-residue civilised diet affecting the venous return from the lower parts of the body is fully satisfying and in line with the general observation that, whilst faulty anatomy is a rare cause of disease, faulty use of the body is a common cause.

Acceptance of his hypothesis brings this condition, which is exceedingly common and is the cause of considerable discomfort and disability, within the effective realm of preventive medicine.

Leaving aside the controversial issue of the extraction-rate in regard to nutritive value of cereals, there now seems to be firm ground for recommending cereals of high extraction-rate not only in the prevention of symptomatic constipation but also in relation to the perhaps unsuspected overloaded colon.

For many of us Surgeon Captain Cleave's paper will represent an added and important reason to recommend as a matter of basic family nutritional health education good-quality whole-grain cereals and a minimum of refined starchy and sugary substances.

Health and Welfare Services Department, Eastbourne. K. O. A. VICKERY Medical Officer of Health.

ANTIMONY DIMERCAPTOSUCCINATE IN URINARY BILHARZIASIS

SIR,—Friedheim and de Jongh [1] found in Liberia that a single intramuscular injection of antimony dimercaptosuccinate (TWSb) stopped the elimination of living ova of *Schistosoma hæmatobium* for a period ranging from one to five months. This led to the concept of a "one dose per month suppressive management of bilharziasis" in endemic areas, where the significance of a parasitological cure is lessened by the heavy chances of reinfection. We have made a pilot trial of "suppressive management".

50 persons who were excreting living and hatching ova of *S. hæmatobium* were selected at random in a village of the endemic area in the Nile delta, and given a single intramuscular injection of TWSb, depending on body-weight: 11–20 kg., 0·3 g.; 21–30 kg., 0·4 g.; above 30 kg., 0·5 g.

The 50 subjects were examined one month after the treatment. None were passing living hatching ova of *S. hæmatobium*; 11 patients passed dead ova (i.e., motionless, granular, opaque, and deformed ova); 39 patients passed no ova at all.

These findings in Egypt confirm the observations made in Liberia and support the view that a single dose of TWSb, repeated at monthly (and possibly longer) intervals, may be expected to suppress the elimination of hatching ova, and thereby remove the patient as a hazard to the public health.

New York. ERNST A. H. FRIEDHEIM.
Department of Tropical Medicine, University of Alexandria. HASSAN H. SALEM.
High Institute of Hygiene, Alexandria, Egypt. ABDEL F. EL SHERIF.

1. Friedheim, E. A. H., de Jongh, R. T. 1959 (in the press).

ACUTE PARENCHYMATOUS GLOSSITIS WITH GANGRENE OF THE TONGUE

SIR,—The condition here described appears to be unique in the annals of surgery. The case has been discussed with many eminent authorities on surgery and pathology, but no-one seems to have heard of anything similar. Isolated patches of gangrene of the tongue may appear in conditions of cancrum oris, but such an example of massive gangrene does not appear in the literature.

The patient, an edentulous female of 74, complained of a pain which started above the angles of the jaws. The pain gradually moved up to the temporal areas on both sides, the right being worse than the left. She noticed heavy sweating at night which continued for two to three weeks. The sweating was so severe that she had to change her nightwear two or three times a night. Aspirin eased the pain but had no effect on the sweating. After three weeks her throat became swollen and congested and she had difficulty in swallowing. After a further two weeks the neck became swollen and her tongue began to swell until it filled the whole of the oral cavity. She was unable to protrude the tongue or to open her mouth more than a quarter of an inch. The condition gradually worsened until, on a night six weeks from the onset, she suffered intense pain and felt she was choking. Her doctor had put her on oxytetracycline but she was unable to swallow the tablets. At this stage one of us (S. H.) was called to see her.

The patient was in great distress, her temperature was 103°, pulse 120, and she was obviously suffering great apprehension from the fact that she was finding it difficult to breathe and could not even take liquids by this time. On attempting to open the jaws it was found that by straining with a spatula about one-third of an inch opening could be obtained, and this revealed a grossly enlarged tongue which completely filled the cavity of the mouth and which was compressing the fauces and soft palate. She complained of great pain in the course of examination.

She was immediately removed to hospital and the aural surgeon (M. D. C.) was called as an urgent tracheotomy would probably be needed. She was immediately given 1 g. of streptomycin parenterally. It was noticed that her breath had a faintly sweetish odour, not in the least offensive.

Further examination showed the surface of the tongue to be covered with dry heaped-up epithelium which could easily be scraped off. Some of this was immediately sent for bacteriological examination. The patient was given an injection of morphine and settled down for the night.

Next day the condition seemed easier. Her temperature was

The condition of the tongue seen after the onset of gangrene. Note profuse salivation.

down to 101°, and some salivation was noted. The tongue itself appeared to have decreased a little and the jaws could be more easily opened. Streptomycin was continued (0·5 g. b.d.). At the end of three days the condition appeared to be improving rapidly but the edges of the tongue were beginning to thin out, and stringy cobweb-like light brown appendages were hanging all round the edges of the anterior two-thirds of the tongue. Salivation now became very excessive, in fact enough to cause some inconvenience to the patient. This slow destruction of the tongue persisted steadily. Part of the cobwebby appendages were sent for microscopic section but showed only completely unidentifiable necrotic tissue. No attempt was made to dislodge any of the appendages by force or by scraping, because that might give rise to uncontrollable hæmorrhage. It seemed safer to allow the process to proceed to its own line of demarcation.

By the end of three weeks the whole of the anterior two-thirds of the tongue had disappeared as far back as the line bounded laterally by the circumvallate papillæ, and in the midline by the foramen cæcum. The patient's condition was now otherwise normal and she was allowed home.

She was visited at home after a week, when she was having the utmost difficulty in maintaining her lower dentures in position without her tongue to depress them. A dental surgeon made plans to design a plate which might adhere more satisfactorily to the lower jaw and floor of the mouth. By this time she had very little difficulty in swallowing either fluids or solids. After a further month she had a new denture which seemed more effective than the old one. Her phonation was remarkably good considering the amount of tongue lost. Labials were pronounced perfectly, the dentals less well. Her main difficulty lay with the liquids and sibilants. Gutturals were normal.

The pathology in this case cannot be accurately determined but it seems that she had an acute infective thrombosis of both the deep or terminal lingual arteries and veins. That the posterior one-third of the tongue was not affected was probably due to its deriving its blood-supply from the dorsales lingual arteries, which arise from the second part of the main lingual artery, and an additional supply from the tonsillar branch of the facial artery. The only organism recoverable during the course of the disease was *Escherichia coli*, so it is surprising that even when the gangrenous process was at its height there was no oral fœtor. The infection appears to have been blood-borne since there was no history of a wound or other excoriation of the tongue.

STANFORD HOWARD
M. D. CREMIN.

Burnley.

AN EXAMINATION PAPER FOR . . . ?

SIR,—In their letter of Aug. 15 Dr. Walther and Dr. Raeburn quote, with hair standing on end, the questions set to nurses in an examination paper, but do not say how they were answered. If the answers are still available and a random sample of them could be scrutinised by a random sample of ex-medical-examiners, their verdict might, perhaps, tempt the authors of this letter to eat their words, or their critics in the nursing world to endorse them.

Sunnfjord, Norway. CLAUDE LILLINGSTON.

SIR,—It is gratifying to learn from your columns and from other sources that the education of nurses is of great controversial interest for both the professions concerned. Sufficient friction will generate light as well as heat.

It is surprising that anyone should put forward the argument that student nurses have not criticised the final exam. paper we quoted. What juniors would dare?

We are happy to learn that a State-enrolled nurse can proceed in due course to become a State-registered nurse, although Professor Vining (Sept. 12) and Dr. Grant (Aug. 29) do not seem to believe that this is possible.

We understand that it is usual for all candidates to pass the type of paper quoted. This only proves our contention that "we can discern nothing which will ensure that the good nurse shall pass and the bad nurse fail". We also understand that most failures occur in the practical exam. This immediately suggests that too much time is perforce given to training in theoretical matters to the exclusion of proper practical experience.

Finally, we note from the letters that there is a division of opinion between nurses and doctors. This leads us to wonder whether the medical profession as a whole is dissatisfied with the present-day trends in the training of nurses.

Whipps Cross Hospital, London, E.11. W. W. WALTHER
C. RAEBURN.

BRITISH ASSOCIATION FOR CANCER RESEARCH

SIR,—It is proposed to form a British Association for Cancer Research in order to bring together cancer research workers in this country and to facilitate the interchange of ideas in this field. With the approval of the British National Cancer Committee, arrangements have been made to hold a meeting in the University of Glasgow from Sept. 15 to 17, 1960. This meeting will be open to all members of cancer research organisations in Great Britain and Ireland, and it is hoped that there will be a representative attendance.

Further details will be available early in 1960.

J. G. BENNETTE
Secretary
E. BOYLAND
J. W. JULL
P. R. PEACOCK
Steering Committee of the Proposed British Association for Cancer Research.

Courtauld Institute of Biochemistry, Middlesex Hospital Medical School, London, W.1.

ADMINISTRATION OF DRUGS IN HOSPITALS

SIR,—In this large geriatric hospital we also are experimenting with fold-flat files ('Kardex', Remington Rand) in controlling the administration of drugs.

The procedure formerly used was that the doctor prescribing or stopping treatment wrote his instructions in the treatment page of the case-sheet. At the same time the ward sister made an entry in her day-book, and later she or the staff-nurse made an appropriate alteration in the ward drug-list, from which the nurse in the medicine round actually worked. This system allowed too many opportunities for errors to intervene between what the doctor intended and what the patient actually received.

Under the new scheme only one record of treatment is made, and only one person—the doctor—makes it. Each patient has a treatment card on which the doctor writes the drug, dose, route of administration, frequency of dosage, and dates of starting and stopping treatment. The cards are kept in the fold-flat file in ward order, and the file is used by the nurse on her medicine round, and is taken on the doctor's ward round. When a patient is put on treatment a coloured signal is attached to his card, and this is removed when treatment is stopped. Three different colours are used for oral, parenteral, and topical treatment. The cards have a gummed strip on the back at the top, and when the patient is discharged his card is taken out of the file and attached to his case-sheet as a permanent record of treatment.

This system is particularly well suited to the needs of a geriatric unit, where perhaps only half the patients receive drug treatment. The nurse on the medicine round sees at a glance which patients are on treatment; the doctor is reminded on every ward round which treatments are still being given; and there is no possibility of discrepancy between different sets of instructions.

While I appreciate that a more detailed scheme, such as that described by Mr. Fowler (Sept. 5), may be

necessary in busy general wards, I cannot agree that the simpler method outlined here need be complicated by the use of carbon copies.

Foresthall Hospital,
Springburn, Glasgow. BERNARD ISAACS.

THESAUROSIS FOLLOWING INHALATION OF HAIR SPRAY

SIR,—We have read with some concern the communication in your issue of Aug. 15 by Dr. Edelston relating to possible health hazards resulting from the use of hair sprays.

We feel that certain points, although mentioned by the author, require more emphasis, particularly the fact that the patient had not used hair sprays for six months when her condition was observed, and also that the composition of the hair spray was unknown but assumed to be based on polyvinyl pyrrolidone. The author does not appear to be aware that many hair sprays are still made from shellac, and that in any case the two American cases reported by Bergmann et al. have given rise to some doubt as subsequent trials and evidence do not support the view that this was a contributory cause.

We would, in particular, wish to draw attention to the recent paper by J. H. Draize, A. A. Nelson, S. H. Newburger, and E. A. Kelley, of the division of pharmacology, Food and Drug Administration, United States Department of Health, Education and Welfare, who have reported an investigation of all types of hair spray, including those based on P.V.P., and conclude that they are completely harmless and give rise to no hazards.

Dr. Edelston's further comments in the light of these later American studies would be welcome. We agree that new materials used in cosmetics require evaluation. We believe that the work carried out in America by Draize and his coworkers represents the type of systematic and controlled evaluation desirable in these cases.

British Oxygen Research and
Development Ltd.,
London, S.W.19. I. GREENFIELD.

SIR,—The evidence for the diagnosis of thesaurosis in the case described by Dr. Edelston (Aug. 15) is tenuous in the extreme, there having been neither respiratory function tests, skin tests, nor any biopsy evidence to support the diagnosis. It seems more probable that this patient was suffering from sarcoidosis which spontaneously resolved and the fact that she used a hair spray two weeks before was fortuitous. The use of hair sprays by women is a fairly common habit.

Section for Pulmonary Diseases,
School of Medicine,
University of Maryland,
Baltimore. WILLIAM K. C. MORGAN.

SIR,—In his report of pulmonary changes described in a single patient, which he attributed to the use of hair sprays, Dr. Edelston mentioned certain reports on this subject from the American literature. I should like to bring your readers' attention to a number of American reports demonstrating the safety of hair spray, which were not included in Dr. Edelston's report. These unbiased studies were scientifically designed for the express purpose of determining whether or not hair sprays were safe for human use; these included clinical,[1] experimental,[1–3] analytical,[1 2] histological [1–3] and radioactive tracer studies.[3] These studies are in marked contrast to a presumptive diagnosis in a single patient.

Following a comprehensive investigation of 6 different hair sprays (on the basis of varied hair fixatives in animals and humans), Draize et al.[1] concluded that the hair sprays produced no adverse effects: " this data from both the human and animal exposures indicate that the ordinary use of aerosol hair spray preparations of the composition and physical characteristics of those included in our studies poses no problem of safety to users ". Calandra and Kay,[2] who studied effects of hair sprays experimentally, including hæmatological studies, urinanalysis, röntgenological studies, and histopathological examination, concluded that " there is no experimental evidence to substantiate the development of pulmonary thesaurosis or pulmonary alveolar proteinosis as a result of the aerosol exposures".

Radioactive tracer studies,[3] using tritiated polymers commonly used in aerosol hair sprays, including histological examination of necropsy tissues in animals following exposures, have also demonstrated absence of any significant thesaurosis which could possibly cause pathological changes.

These reports clearly demonstrate that hair sprays are safe for general use.

LESTER I. LEONARD
Medical Director, Research and Development,
New York. Revlon, Inc.

THE MECHANISM OF MIGRAINE

SIR,—Your comments in an annotation of April 4 were of great interest to me. Some observations which we have made may pertain to your concluding query, " what throws the migrainous mechanism into activity ?"

We have reason to believe that this question, restated, may lead to answers which may have theoretical as well as therapeutic implications. It is proposed that the following question be considered: " What interferes with the homœostatic mechanism which maintains cerebral vessels midway between extreme vasoconstriction and excessive vasodilation ?"

Our observations on migraine have occurred fortuitously as a result of extended studies of respiratory alkalosis in cases of anxiety. We have found that when anxiety is associated with hyperventilation, the patient is confronted with an array of additional distressing symptoms which are secondary to carbon-dioxide deficit. These symptoms feed back and accentuate anxiety. They can be interrupted almost immediately by inhalation of 5–7% carbogen (oxygen with 5% carbon dioxide). Furthermore, thrice-daily 5-minute inhalations are remarkably effective in inhibiting further attacks of hyperventilation. We speculate that overloading the respiratory centre with carbon dioxide tends to " set " this centre at a lower level of sensitivity. The resultant shift in the respiratory component of the acid-base equilibrium is thought to be responsible for the marked diminution of those symptoms such as dizziness, muscular hypertonus, and tremulousness which are characteristic of many anxiety states.

Accidentally, in the psychiatric field, we see patients occasionally with syndromes which are properly within the purview of neurology. A dozen patients with classical migraine have presented themselves to us during the past five years. We found ourselves unable to resist the temptation to experiment on them. They were equipped with our regular carbogen inhalation apparatus and instructed to inhale this gas at the onset of aura. Almost without exception, the aura disappeared and the expected cephalalgia did not materialise. The patients were instructed to pursue 5-minute thrice-daily inhalations, according to the procedure which had been established in anxiety cases. Recurrences of even the aura of migraine were rare. When regular carbogen inhalations were discontinued, migraine attacks usually failed to reappear for months or years and often indefinitely.

Perhaps the question you raised and we restated has a partial and provisional answer. Under non-pathological conditions, cerebral and perhaps other vessels are maintained by homœostasis between mild and temporary vaso-

1. Draize, J. H., Nelson, A. A., Newburger, S. H., Kelley, E. A. *Proc. Scientific Section, Toilet Goods Association*, 1959, **31**, 28.
2. Calandra, J., Kay, J. A. *ibid.* 1958, **30**, 41.
3. Bogner, R. et al. To be published.

dilation. Certain factors extraneous to the carotid tree, among them respiratory alkalosis, tend to induce a severe and continuing vasoconstriction. Finally the arteriolar muscles become totally exhausted and the vessels spring into complete dilation, with resultant stimulation of pain end-organs in the vessel walls.

Stanford University School of Medicine,
Francis Memorial Hospital,
San Francisco. JAMES A. HAMILTON.

REINFUSION OF ASCITIC FLUID

SIR,—After reading the interesting report by Dr. Pálos and Dr. Antalóczy,[1] we decided to try using the reinjection-of-ascitic-fluid techniques they described to treat patients with ascites due to gross hepatic enlargement associated with longstanding schistosomiasis or chronic malnutrition. We selected five cases ranging in age from about 20 to over 60 years—ages being more a matter of rough estimate than accurate knowledge.

Each patient was reinjected with 160 ml. on each of five separate occasions and each reinjection followed paracentesis abdominis performed on the same day. One patient suffered a mild reaction which was controlled by anti-histamines, and one ran away after her fourth reinjection.

Unfortunately we have no means of measuring blood chemistry, so our results depend entirely on clinical impressions rather than on accurate determination. Nevertheless, in two of the cases, both middle-aged, the ascites gathered at a much slower rate at the end of the course than at the beginning, and in one of these two there was no clinical ascites at all at discharge several days after the end of the course. In three cases there was no obvious improvement at all.

It would be helpful to follow-up such cases; but, though we have made arrangements to do so, there is small likelihood that we shall see them all again.

Arua, Uganda. T. R. CULLINAN.

GENERAL PRACTICE

SIR,—Professor Eckstein, whose book you have so ably summarised in *The Lancet* of Sept. 12, and Dr. Godber (Aug. 29), both re-emphasise the well-worn thesis that the future of general practice lies in the health centre, with group practice working therein.

The encroachment into the sphere of general practice, which is giving increasing anxiety to so many general practitioners, can be limited and set in reverse only by health-centre practice. The fears that the report of the Cranbrook Committee have aroused would not have arisen if group practice existed in health centres incorporating the work now done by the local-authority clinics. The general practitioner who was not a G.P.-obstetrician would not "lose" his patient if his colleague in the centre with whom he was in daily touch was carrying out the antenatal supervision. The demand for geriatric guidance centres (Sept. 12, p. 334) would not arise if the general practitioner with the facilities of a health centre, the leader of a team of ancillary health workers, were available in every locality.

Dr. Godber emphasises the need for more consultations between the specialist and the general practitioner, and no doubt some of these could take place at the health centre, thus relieving the hospital outpatient departments, while a practitioner who had access to laboratory and X-ray facilities would be in a better position to meet the specialist on equal ground and the meeting would be a true "consultation".

Professor Eckstein explains why the profession which had voted in the B.M.A. questionary overwhelmingly in favour of health centres subsequently voted against Government proposals that embodied them; it was their instinctive fear of non-medical intrusion into medical affairs and their fear of loss of clinical freedom. Now that ten years of the N.H.S. have been experienced which have not in the main borne out those fears is it not time to act in the defence of general practice and to demand that health centres should be provided in sufficient numbers to be really experimental, so as to work out in practice how they can best be administered to ensure continued clinical freedom and professional independence?

Birmingham. M. BARROW.

1. *Lancet*, 1959, i, 525.

HYPERVENTILATION FOR THE MAINTENANCE OF ANÆSTHESIA

SIR,—The article by Dr. Geddes and Dr. Gray (July 4) raises some controversial issues both theoretical and practical.

The presence of delta waves in an electroencephalogram is, according to some, no more a criterion of "depth" of anæsthesia than unconsciousness is. Martin et al.[1] point out that one can discern 7 electroencephalographic levels of anæsthesia: (1) fast rhythm, (2) rhythmic slow waves of high potential, (3) complex mixed rhythm, (4) early burst suppression, (5) moderate burst suppression, (6) severe burst suppression, (7) complete suppression. Correlation, however, of these phases with the behaviour of the patient and his reflexes to traumatic surgical stimuli is neither uniform nor precise under various conditions and agents (and that applies to the presence or absence of either hypocapnia or hypercapnia). They conclude, in fact, that "in a broad sense the electroencephalogram alone is no more valid a criterion of 'depth' of anæsthesia (which 'depth' needs a precise definition) than is the manifest change in the pattern of any single physiologic system, such as oculomotor, the respiratory or the cardiovascular system". On the other hand, pronounced induced hypocapnia seems to produce one very definite effect—namely, cerebral vasoconstriction and diminished perfusion of the brain. Lassen [2] states quite clearly:

> "Subnormal alveolar and arterial pCO_2 values cause a pronounced cerebral vasoconstriction. Hypocapnia produced by marked hyperventilation has been found to decrease cerebral blood flow to about 60% of the resting value. It is interesting that this is the same critical level of cerebral perfusion as was found in severe hypotension with clinical signs of cerebral hypoxia. This indicates that cerebral symptoms produced by hyperventilation may be partially caused by cerebral hypoxia (*which incidentally may also produce slow high voltage waves* [my italics]) in addition to the more direct effect of the low arterial pCO_2 on cerebral cells."

Now we come to the subject of alternating positive-negative phase of controlled respiration. Here again a voice of warning comes from Lynch et al.[3] They clearly state on the strength of experimental evidence on human beings that controlled respiration with negative phase produces narrowing of small intralobular bronchi, increased air resistance, and diminished lung compliance. Their opinion is that these changes deserve serious consideration and may be harmful by causing hypoventilation even in normal patients.

This newly described hazard, in conjunction with the already known ones of air trapping and alveolar collapse that may occur in the emphysematous lung, invite further investigation of the merits or otherwise of the use of negative pressure during expiration.

When the method described by Dr. Geddes and Dr. Gray is advocated universally even for such operations as herniorrhaphy or hæmorrhoidectomy one is tempted to ask: is this really necessary? The foregoing opinions of various workers make one wonder. When one thinks,

1. Martin, J. T., Faulconer, A., Jr., Bickford, R. G. *Anesthesiology*, 1959, **20**, 359.
2. Lassen, N. A. *Physiol. Rev.* 1959, **39**, 200.
3. Lynch, S., Levy, A., Ellis, K. *Anesthesiology*, 1959, **20**, 325.

however, of an elderly arteriosclerotic emphysematous patient undergoing a lengthy gastrectomy, one may be forgiven for expressing some misgivings: is this really the safest method? Have the reported (and unreported) cases of so-called irreversible curarisation any connection with these physiological mechanisms?

London, N.W.6. BERNARD KENTON.

SIR,—Dr. Geddes and Professor Gray, in their article of July 4, have shown that hyperventilation with N_2O and O_2 produces a state which, by E.E.G. monitoring, is indistinguishable from anæsthesia obtained by ether and halothane. They also state that autonomic reflexes are not completely abolished even by deep ether anæsthesia. It would thus seem that, with hyperventilation, effects could still be produced by gross autonomic stimulation.

As I have previously stated,[1] I find that reactions sometimes do occur during hyperventilation anæsthesia when the surgeon is cutting and pulling on autonomic plexus areas in the upper abdomen and pelvis. Patients having reactions presumably have a high autonomic tone and are usually young and fit; one rarely sees them in the old and very ill. These reactions can be prevented by local anæsthesia injections into the autonomic pathways of the organ or area concerned.

I should like to suggest that patients, in whom experience has shown reactions are likely to occur, should have the benefit of hyperventilation anæsthesia in addition to autonomic isolation of the organ being operated upon by means of well-placed local anæsthesia.

Peterborough Memorial Hospital, Peterborough, Northants. R. E. LODER.

DEATH AFTER FIRST TREATMENT WITH ELECTROPLEXY, THIOPENTONE, AND SUXETHONIUM BROMIDE

SIR,—I should be interested to know whether any readers have had experience of a case similar to the one that follows.

A woman of 52 with a depressive anxiety state was referred for outpatient modified electroplexy on May 12, 1959.

She was in good physical state. Blood-pressure 160/90 mm. Hg, heart normal, vessels soft, pulse good volume and regular. Other systems normal. Atropine gr. $^1/_{50}$ was given thirty minutes before treatment. Thiopentone 0·2 g. was followed by suxethonium bromide ('Brevidil E') 0·08 g. Relaxation was satisfactory and modified convulsion was induced at 3.15 P.M. Breathing commenced but was very shallow and the patient soon became cyanosed. Oxygen was given and her colour soon became normal, but respirations remained very shallow. Ventilation was continued.

4.15 P.M.: blood-pressure had fallen to 110/80, respirations practically imperceptible, intramuscular nikethamide and O_2 and 5% CO_2 were given.

5 P.M.: pulse 70, respirations unchanged, B.P. 110/80, ventilation continued and artificial respiration.

6.40 P.M.: patient commenced shallow irregular breathing. O_2 and CO_2 mixture continued.

7.45 P.M.: breathing remained very shallow, and ceased when O_2 was discontinued. Transfusion was considered, but in view of improvement at 6.40 P.M. it was thought advisable to continue the same regime. However, at 8 P.M., colour became very pale, skin cold and clammy, B.P. 98/75, pulse 88, no fibrillation. Nikethamide repeated. Breathing continued to be shallow and irregular until 8.15 P.M., when she became very pale, respirations ceased entirely, and death occurred at 8.20.

Postmortem examination revealed pulmonary œdema, coronary atheroma, and myocardial fibrosis.

Although death has been reported with thiopentone, suxamethonium, and E.C.T., I cannot find any report of death after E.C.T. with suxethonium and thiopentone.

Subsequent discussion with colleagues about the emergency treatment of collapse following electroplexy with suxethonium suggested that treatment based on a letter by Foster [1] should be tried. On this basis the lowering of potassium chloride in such cases is replaced as follows: 20 ml. of 20% potassium chloride and 30 ml. of calcium gluconate in 500 ml. of normal saline are given by intravenous drip over a maximum period of fifteen minutes. This method of treatment can be available in centres where electroplexy is administered.

Warley Hospital, Brentwood, Essex. F. A. CAMPBELL.

ANKARA CATS

SIR,—In recent conversation with Dr. M. Coruh, of Turkey, I was learning about the fauna of his country. He mentioned Ankara cats which have long white hair and eyes of different colours. Being reminded of the white forelock and heterochromia iridum of Waardenburg's syndrome [2] I inquired whether these cats are congenitally deaf. They are. It is possibly for this reason that they are lazy and do very little hunting. This information may be of interest to research otologists.

Alder Hey Children's Hospital, Liverpool. R. W. SMITHELLS.

THE MEDICAL SUPERINTENDENT

SIR,—In the Belmont Hospital experiment described in *The Lancet* of Aug. 22 (p. 170), the medical administrator was proposed by the medical staff committee but the appointment was made by the regional hospital board upon the advice of the hospital management committee. It has been made clear, both at the time and since, that the medical administrator is in no way to act as the agent or representative of the medical staff. The point is emphasised because your leader suggests that many, especially static, mental hospitals would be well served by this type of administration, whilst the more dynamic hospitals will fare better under the guidance of a "great superintendent".

The majority of both medical and lay administrators are in my experience strongly opposed to hospital management by a medical committee, on the grounds that such a committee cannot cater for the needs of the community as a whole, nor could it deal adequately with a lay administrator or committee. It seems that as far as administration is concerned the mental hospitals have reached the stage held by the municipal general hospitals before the war. In an earlier leader [3] you made the point that the Russians prefer public enterprise and public responsibility, but we attempt to retain personal responsibility whilst getting the benefit of public enterprise. You deplored the heirarchy in which most doctors work in the State medical services of the peoples' republics. Has an attempt yet been made to organise a psychiatric hospital without a father or an uncle, and, if so, was the retribution so terrifying that the story cannot be told?

A. S. THORLEY
Chairman,
Belmont Hospital Medical Staff Committee.

Belmont Hospital, Sutton, Surrey.

1. Loder, R. E. *Lancet*, 1957, ii, 468.

1. Foster, P. A. *Brit. med. J.* 1956, ii, 1485.
2. Waardenburg, P. J. *Amer. J. hum. Genet.* 1951, **3**, 195.
3. *Lancet*, 1959, i, 29.

A CONCENTRATION METHOD FOR THE RAPID DEMONSTRATION OF MICROFILARIÆ IN PERIPHERAL BLOOD

SIR,—Although filariasis is seldom seen in this country, it is occasionally necessary to diagnose the condition in persons returning from torrid zones. So far as the demonstration of microfilariæ is concerned, methods include the making of stained thick films and the use of wet preparations, the results of the latter being improved by some means of concentration.

The usual methods were tabulated by Harris and Summers,[1] and they described their own rapid technique which gave good results. Briefly, this method involves hæmolysing a sample of venous blood and preparing wet films after centrifugalisation so that motile microfilariæ can be demonstrated.

Gordon and Webber[2] describe another method which requires filtration of the hæmolysed blood through a special cone after the addition of formalin; the sediment and washing are centrifugalised for the preparation of thick films. The literature, however, seems to contain no account of a rapid and simple method for preparing permanent stained films of microfilariæ when they are present only in small numbers in the peripheral blood.

The method here described has the merit of simplicity and was used during the investigation of a patient infected with loa loa. When the patient was first seen microfilariæ were readily demonstrable in thick films stained with diluted Giemsa, but on a second occasion they could be found only with difficulty and after prolonged search. At this time the following method was tried:

5 ml. of venous blood is collected and placed in a bijou bottle containing sequestrene or Heller and Paul's mixture. The blood is allowed to sediment without disturbance and the plasma is then withdrawn by means of a pasteur pipette and placed in a round-bottomed centrifuge tube with an internal bore of about 8 mm. Using an angle centrifuge the plasma is spun at 3000 r.p.m. for 5 minutes, and the supernatant plasma is then discarded. The sediment consists of leucocytes, platelets, a few red cells, and the microfilariæ. Using a pasteur pipette, a portion of the sediment is withdrawn and rubbed gently on a slide so that a thick film about the size of a shilling is made. This dries in the air within a few minutes and is then stained by Leishman's method as for thin blood-films. After staining, the film must be allowed to dry in air, when it is mounted in oil for examination under the low power of the microscope. If the film has been correctly made the leucocytes and platelets will not interfere with the ready identification of the microfilariæ.

In order roughly to assess the degree of concentration and the general value of the method three films were prepared and compared with three thick films of similar size (*a*) from fresh whole blood, and (*b*) from sedimented red cells. The thick films were sloped and allowed to dry slowly in air, and were then stained for four hours with diluted Giemsa. The whole of each film was carefully and systematically examined for microfilariæ and the number seen by low-power examination was as follows:

	Thick film of whole-blood sediment	*Thick film of red-cell sediment*	*Centrifugalised deposit from plasma*
Slide 1	0	1	7
Slide 2	1	0	12
Slide 3	0	2	9
Total	1	3	28

It is not possible to judge the true value of this method from examination of a single patient but the figures suggest that it is worthy of further trial by those who are in a position to examine more. Apart from concentration the method has several advantages over the usual thick-film technique; the film does not have to be dried for a long time, staining involves fixation and is more rapid than is possible with diluted Giemsa, the film does not tend to wash off, and finally the non-hæmolysed cellular deposit forms a pleasing background for contrasting the microfilariæ.

Central Laboratories, Portsmouth. F. C. STALLYBRASS.

1. Harris, J. S., Summers, W. A. *Amer. J. trop. Med.* 1945, **25**, 497.
2. Gordon, R. M., Webber, W. A. F. *Ann. trop. Med.* 1955, **49**, 80.

NAMES FOR BLOOD-CLOTTING FACTORS

SIR,—Like other workers, I have often been confronted with the difficulties deriving from the use of various terms to describe the blood-clotting factors, which you describe in your annotation (May 30).

About two years ago, in a paper submitted to the University of Athens, I suggested that this terminology should be simplified by using the letters of the Greek alphabet. If accepted, this new nomenclature would also have the advantage of making clear the distinction between the factors physiologically existing in the blood on the one hand, and factors produced during the process of blood coagulation on the other.

After further consideration, I think now that a combined use of the Greek and Latin alphabets would be the more appropriate system of defining these factors.

My proposal is that the factors physiologically existing in the blood should be described by the capital letters of the Latin alphabet, and that the factors produced during the process of blood coagulation should be represented by the corresponding small letters of the Greek alphabet.

Proposed symbol	Name* of factors physiologically existing in the blood	No.	Proposed symbol	Name* of factors produced during the process of blood coagulation	No.
A	Platelets		α	Prothromboplastin	
B	Calcium	IV	β	Thrombocalcin	
C	Thromboplastinogen	VIII	γ	Thromboplastin	III
D	Proconvertin	VII	δ	Convertin	
E	Prothrombin	II	ϵ	Thrombin	
F	Proaccelerin	V	ϕ	Accelerin	VI
H	Fibrinogen	I	η	Fibrin	
I	Christmas-factor	IX	ι	.....	
K	.....		κ	.....	
L	.....		λ	.....	

* I mention the factors by their names used in Greece. For complete list of synonyms see Marbet, R., Winterstein, A. Synonyma der Gerinnungsfaktoren, Thrombose und Embolie; p. 53. Basel, 1954.

Some of the advantages of the proposed system are:

(1) The present confusion is eliminated.

(2) The relation between factors physiologically existing in the blood and factors produced during the process of blood coagulation is obvious.

(3) In writing the difference between the two alphabets makes any confusion impossible.

(4) In speech the difference in pronouncing the letters of the two alphabets eliminates the need of further clarification which would be necessary if the letters of only one alphabet were used (A and α, pronounced *ei* and *alpha*. Otherwise it would be necessary to define *ei* capital and *ei* small).

Athens. G. K. LAZANAS.

Appointments

BEVERIDGE, MAHALA M., L.R.C.P.E.: assistant venereologist (S.H.M.O.), Sheffield area clinics.

CROWLEY, P. J., M.D. Cantab., D.P.M.: part-time consultant children's psychiatrist, Rotherham-Doncaster area hospitals.

DEACON, MARIE M., M.B. St. And.: assistant school M.O., Stoke on Trent.

DEWAR, D. A. E., M.B. St. And., F.F.R., D.M.R.D.: consultant radiologist, Dundee general hospitals.

KAPUR, SAROJ, M.B., D.C.H.: assistant school M.O., Stoke on Trent.

PYKE, D. A., M.D. Cantab., M.R.C.P.: physician to outpatients, department of diabetes, King's College Hospital, London.

Colonial Appointments:

BARR, D. M., M.B. Glasg.: M.O., Barbados.
BURCHILL, J. B., M.B. Brist.: M.O., Somaliland.
MILLER, C., L.S.M.F. Lucknow: M.O., Sierra Leone.
PALMER, T. I., L.M.S.S.A.: district M.O., St. Vincent, Windward Islands.
RHODES, J. D., M.B. Manc.: M.O., Jamaica.
ROWLEY, R. K., M.B. Birm.: M.O., Barbados.
SHUN-SHIN, MAXIME, M.B. Lond., D.T.M. & H.: specialist (surgery), health department, Mauritius.
SPICER, H. J. M., M.B. Aberd.: house-officer, Trinidad.
THOMSON, J. M., M.B. Aberd.: M.O., Tanganyika.

Notes and News

HOSPITAL STATISTICS

THE start of the National Health Service offered a congenial climate for other beginnings, and in 1949 the Ministry of Health and the General Register Office joined forces to launch a tentative inquiry into national morbidity based on statistics about hospital inpatients. After three fluid experimental years the procedure of the inquiry hardened into a more permanent pattern, and in 1952 a modified "inquiry" was started based on a 10% sample of discharges from all hospitals (excluding the mental hospitals). Relevant new questions, such as waiting-time and source of admission, were added to the form of inquiry. To begin with, the returns were, not unnaturally, incomplete and patchy, and though they were analysed the results were not published. But the returns have steadily improved, and by the end of 1957 the inquiry covered practically all discharges from all hospitals in England and Wales. The returns of even some of the earlier years were comprehensive enough to repay the publication of their analyses and those of 1955 were chosen as a starting-point,[1] partly because in that year for the first time two regions, Wales and East Anglia, both sent complete returns. Their statistical integrity permits comparison and shows the kind of question which the records of the later years will answer for the whole country. For example:

Greater frequency of hospital treatment for tuberculosis in Wales than in East Anglia confirms the real difference in incidence shown by notification and mortality figures. The discharge-rate for carcinoma of the lung was, on the other hand, higher in East Anglia than in Wales. Peptic ulcer showed higher rates for men than for women in both regions, but acute appendicitis was a commoner cause of admission in Wales than in East Anglia. Discharge-rates for squint in children were higher in East Anglia than in Wales; rates for diseases of the ear were higher in Wales. Urban residents had higher discharge-rates for hernia than rural residents in both regions There were higher rates in Wales than in East Anglia for prolapse of uterus in women and injuries in men.

Readers of the Cranbrook report will also find much of interest in the section on maternity cases. For instance, though the national mean length of stay after delivery was 11 days, it varied from 9 days in Newcastle to 13 days in the South Western Region. Though the normal lying-in period is generally thought to be 10 days, a third of the mothers were in fact discharged sooner, and 7% on or before the seventh day after delivery. Some of these answers are not unexpected, but confirmation as well as information is always valuable, especially in what we hope will be a flamboyant period of hospital building.

University of Leeds

On Thursday, Sept. 24, at 3 P.M., at the University, Prof. Francis D. Moore, of the Peter Bent Brigham Hospital, Boston, Massachusetts, will give the Moynihan lecture. His subject will be Britain and America.

University of Manchester

Prof. A. C. B. Lovell will give the Lloyd Roberts lecture on Friday, Oct. 23, at 5.15 P.M., when his subject will be the Structure of the Universe.

University of St. Andrews

Dr. H. C. Fowlie has been appointed lecturer in psychiatry in Queen's College, Dundee.

Institute of Diseases of the Chest, London

Clinical demonstrations for doctors will be arranged by Dr. N. Lloyd Rusby on Fridays from Oct. 2 to Dec. 11. Open lectures will be given on Wednesdays from Oct. 7 to Dec. 9, by Dr. F. Lee Lander, Dr. D. T. Carr, Mr. V. C. Thompson, Dr. F. H. Scadding, Dr. Lynne Reid, Mr. H. R. S. Harley, Mr. T. Holmes Sellors, Dr. R. V. Gibson, Mr. N. R. Barrett, and Mr. M. Paneth. All the lectures will be held at 5 P.M., at the institute, Brompton Hospital, Fulham Road, S.W.3.

1. The Registrar General's Statistical Review of England and Wales for 1955, Supplement on Hospital In-patient Statistics 1959. H.M. Stationery Office. Pp. 206. 10*s*. 6*d*.

British Medical Association

On Oct. 28, at 3 P.M., at B.M.A. House, Tavistock Square, London, W.C.1, Prince Philip, Duke of Edinburgh, will be installed as president of the Association, and will deliver the presidential address. He will also preside at a dinner on the same day at 7.30 P.M. in Guildhall.

The Association is offering the following research scholarships:

Ernest Hart memorial scholarship (£300), Walter Dixon scholarship (£300), and four ordinary scholarships (£200) for research in any subject (including State medicine) relating to causation, prevention, or treatment of disease; Insole scholarship (£250) for research into the causes and cure of venereal disease.

The scholars need not be engaged full-time. Applications must be submitted by March 1, 1960. Further particulars may be had from the secretary of the Association, B.M.A. House, Tavistock Square, London, W.C.1.

Royal Medico-Psychological Association

Prof. Alfred Meyer will deliver the Maudsley lecture to this Association at 1, Wimpole Street, London, W.1, on Thursday, Nov. 12, at 2.15 P.M. He will speak on Emergent Patterns of the Pathology of Mental Disease.

Medical Protection Society

The annual general meeting of this society will be held at Victory House, Leicester Square, London, W.C.2, on Wednesday, Oct. 7, at 3 P.M.

Medical World General Practice Conference

This conference will be held on Sunday, Oct. 18, in the Victoria Halls, Bloomsbury Square, London, W.C.1. The subjects for discussion are business methods in general practice, problems of an ageing population, the domiciliary mental service, and an inquiry into general practice. Further particulars and tickets (10*s*. 6*d*.) may be had from the conference organiser, *Medical World*, 56, Russell Square, W.C.1.

London Medical Exhibition

This exhibition will be held at the Royal Horticultural Society, London, S.W.1, from Nov. 16 to 20, from 11 A.M. to 6.30 P.M., and on Thursday, Nov. 19, to 7.30 P.M. Sir Daniel Davies will open the exhibition on Nov. 16, at 11.30 A.M.

On Thursday, Oct. 1, at 3 P.M., Lord Denning will give the inaugural address to Charing Cross Hospital Medical School at the Royal College of Physicians of London, Pall Mall East, S.W.1.

Dr. T. H. Whittington will give a course of lectures on aspects of refraction work, at the Royal Eye Hospital, London, S.E.1, on Thursdays at 5.15 P.M. from Oct. 15 to Dec. 3, and Jan. 7 to Feb. 4.

The North Western Thoracic Society will hold a meeting on Thursday, Oct. 8, at 5 P.M., at the Clinical Sciences Building, York Place, Manchester, when Dr. Eric Smith will give his presidential address, which is entitled Chest Diseases in Biblical Times.

Rehearsals of the London Medical Orchestra will resume at Cosway School, Cosway Street, N.W.1, on Thursday, Sept. 24, at 7.45 P.M. The hon. secretary is Dr. H. O. Engel, c/o Ford Motor Co. Ltd., Dagenham.

The annual dinner of past and present men students of the Leeds Medical School will be held at the Griffin Hotel, Leeds, on Friday, Oct. 30, at 7.30 P.M. Tickets (27*s*. 6*d*.) may be had from the hon. secretary, dinner committee, Leeds Medical School.

The Doctors' Hobbies Exhibition will be held at B.M.A. House, Tavistock Square, London, W.C.1, from Nov. 16 to 20. Entry forms may be had from the Public Relations Department, Benger Laboratories Ltd., Holmes Chapel, Cheshire. Entries close on Sept. 23.

Comments on the draft British Standard for Metal Surgical Implants, Drills and Screwdrivers used for Bone Surgery (CZ[SGC]9568) should be sent by Oct. 5 to the British Standards Institution, British Standards House, 2, Park Street, London, W.1.

CORRIGENDUM: *Sympathectomy*.—In our review (Sept. 5) of this book by Dr. P. A. G. Monro we remarked that the case-histories did not mention the age and sex of the patients. Dr. Monro points out that the age and sex of all patients are shown in tables I, II, and III (pp. 94-97) and the ages again in table IX (explained in the text on p. 202).